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MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

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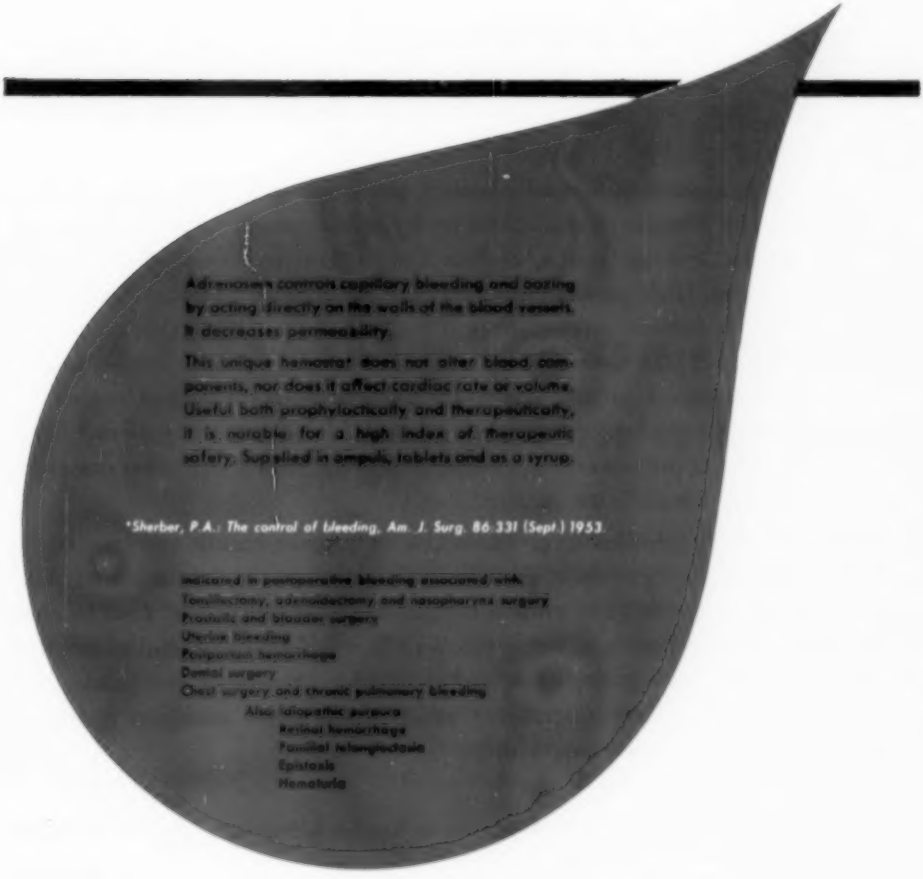
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2. Marquardt, G. H.; Cummins, G. M., and Fisher, C. I.: Blood Protein Replenishment in Treatment of Nephritic Edema, Quart. Bull. Northwestern Univ. M. School *26*:140 (1952).
3. Kark, R. M.: Low Sodium and High Protein Diets in Laennec's Cirrhosis, M. Clin. North America *35*:73 (1951).
4. Kekwick, A.: Protein Deficiency in Surgical Patients, Ann. Roy. Coll. Surgeons England *7*:390 (1950).
5. Stieglitz, E. J.: Nutrition Problems of Geriatric Medicine, Report of Council on Foods and Nutrition, J.A.M.A. *142*:1070 (Apr. 8) 1950.

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[1] *Smith, C. R.: Disinfectants for tuberculosis hygiene, Soap and Sanitary Chemicals 27:130 (Sept.) 1951; 27:145 (Oct.) 1951.*

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*1. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, Prepared with Collaboration of the Committee on Therapeutic Nutrition, Food and Nutrition Board, National Research Council, Baltimore, Waverly Press, 1952.*

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# OBSERVATIONS ON AN EPIDEMIC OF CUTANEOUS AND LYMPHATIC TUBERCULOSIS WHICH FOLLOWED THE USE OF ANTI-TYPHOID VACCINE[1]

MASASHI TAMURA, G. OGAWA, I. SAGAWA, AND S. AMANO

With the Editorial Assistance of Gerald E. Muehsam[2]

(Received for publication April 26, 1954)

## INTRODUCTION

In May, 1946, a large number of children in a Japanese school received two injections of anti-typhoid vaccine. Approximately one-sixth of these vaccinated children developed cutaneous and lymphatic tuberculosis in the months immediately following vaccination. The site of the initial cutaneous lesions coincided with the general area in which the anti-typhoid vaccine had been administered. Due to the exigencies of the times, many facets of this series of happenings could not be completely elucidated. In particular, when the tuberculous lesions appeared, it was not possible to obtain the anti-typhoid vaccine for study and, hence, the presence of *M. tuberculosis* in the vaccine was never demonstrated. Nevertheless, the sequence of events was sufficiently suggestive to warrant the reporting of the entire episode in detail.

## OBSERVATIONS

Six hundred and thirty-one primary school children at the Dojo Primary School in Hyogo Prefecture were inoculated with two courses of typhoid vaccine. These

[1] From the Hyogo National Sanatorium, Miwa-cho, Arima-gun, Hyogo Prefecture, and the Institute for Tuberculosis and Pathological Department, Kyoto University, Japan.

[2] The original manuscript, submitted to the REVIEW by Dr. Tamura and his associates, consisted of an extremely detailed presentation of the observations described in the present report. Because of space limitation, it was not possible to publish the manuscript as originally submitted. Accordingly, with the permission of Dr. Tamura and his associates, the original manuscripts (actually two in number) were turned over to Dr. Gerald E. Muehsam of the Veterans Administration Hospital, East Orange, New Jersey, for reorganization and condensation. Both the authors of the manuscript and the editor of the REVIEW wish to express their appreciation to Dr. Muehsam for his very considerable contribution to the publication of this report.—*The Editor*

inoculations were given on May 6, 1946, and on May 13, 1946, and consisted of 0.3 to 0.5 ml. for the first injection and 0.5 and 1.0 ml. for the second injection of a typhoid and paratyphoid AB mixed vaccine. All injections were made into the upper arm on either the left or right side, and no unusual immediate reactions were noted.

The inoculations were performed by three people. Two were nurses; the third was a woman physician who subsequently was found to be suffering from pulmonary tuberculosis, with acid-fast bacilli in the sputum (Gaffky VI). Efforts were subsequently made to identify the strains of tubercle bacilli isolated from the affected school children as well as from the physician, and both strains possessed the characteristics of human tubercle bacilli. No more specific identification, however, could be established.

Subsequent chest roentgenograms were obtained of the affected children after the appearance of the cutaneous tuberculosis. The tuberculin used was prepared from a tuberculin solution diluted two thousand times and injected intracutaneously in a dosage of 0.1 ml. The presence of a skin erythema larger than 10 mm. in diameter forty-eight hours after the injection was regarded as a positive reaction.

Westergren's method was used for the determination of erythrocyte sedimentation rate, and values at one hour at room temperature were determined.

The bacteriologic study of tubercle bacilli was carried out on culture media made according to the method of Oka-Katakura.

### *Occurrence of Tuberculosis*

Of the 631 children inoculated with the double course of typhoid vaccine, 102 children (16.1 per cent) showed either local or lymph node changes which will subsequently be described. The distribution was approximately equal between both sexes. It is of interest that, of the 102 children affected, 44 were in the third year class of the primary course, 3 were in the Girls' Youth School, but no children in the second-year class of the senior course were affected.

Eighty-three of the 102 infected children remembered the injections, and they recalled that 35 were twice inoculated by the woman physician; 37, once; whereas, the remaining 11 were inoculated by the two other people. Also of interest is the fact that the woman physician, who subsequently was discovered to have chronic pulmonary tuberculosis, performed the typhoid vaccinations in another school, using the vaccine produced by the same laboratory, but that no cases of tuberculosis were found there.

*Types of reaction:* The types of reaction could be grossly classified into three varieties. The first was a swelling and induration near the local site of inoculation, the second was subcutaneous involvement proximal to the site of inoculation and presumably in the path of lymphatic vessels, and the third was involvement of the ipsolateral, axillary lymph nodes.

All of the 102 children developed induration and swelling of the upper arm near the site of inoculation, but only 101 patients could be followed. Nearly one-half developed these lesions approximately one month after the vaccination, although the remainder developed the lesions four to six months later. The longest

time interval between inoculation and the development of a local lesion was six months, except in one case in which the child did not develop a lesion until twelve months later.

The lesions were in the form of local swelling, occasionally associated with a slight degree of temperature elevation. There was a slowly developing induration of the skin accompanied by perifocal erythema, with subsequent softening of the induration. At approximately the time when the softening took place, axillary lymph node involvement developed. Only one child had axillary lymph node involvement prior to the development of the local lesion.

Eight children had spontaneous ulceration of the area of induration. Several of these required incision and drainage, and these subsequently required between one and several months to heal. The healing occurred by scar formation. A number of local skin lesions extended through the subcutaneous tissue into the underlying muscle and, although the superficial lesion was often not larger than pea size, the underlying deeper involvement extended for a considerably greater distance.

Forty patients developed subcutaneous involvement proximal to the local areas of induration and subsequent to it. In only 6 of these was lymphangitis definitely demonstrable. In the others, these subcutaneous lesions appeared to have no direct contiguity with the initial focus. In general, the secondary subcutaneous foci resembled those seen at the primary site, and several of them extended into the deeper underlying tissues. The duration of development of these subcutaneous foci varied from one month to two years and two months after the primary inoculation.

Regional axillary lymphadenopathy occurred in every child who developed the local reaction. In one case this swelling antecesded the appearance of the local lesion, but in most instances it followed the local lesion in one to several months. Three of these groups of axillary lymph nodes ruptured spontaneously, whereas 8 of them required extirpation. Following either extirpation or an uncomplicated course, the axillary nodes slowly decreased in size during a variable long period of time.

For purposes of comparison, the axillae of 106 tuberculin-negative school children were examined. Two-thirds of these had one to two small, pea-sized, axillary lymph nodes on either one or both sides. Only three of these nodes were somewhat larger, and no evidence of drainage or rupture could be found in them.

*Tuberculin reaction:* It is of interest to note that the children at the Dojo Primary School were tuberculin tested in October, 1944. At that time the percentage of positive reactors ranged from 13.7 to 18.5 per cent (varying according to school years), and the mean value was 15.9 per cent. The tuberculin testing was repeated at the end of 1946 and in early 1947, and at this time (seven to eight months following the typhoid vaccination) the average percentage of positive tuberculin reactors was 38.3 per cent.

The highest group in the third year of the primary school had a 70.7 per cent average of positive reactions.

The 102 pupils who developed local or axillary lymph node reactions to the

typhoid vaccine were all shown to have a positive tuberculin reaction. Further, the local reactions appeared in 3 of 51 children who were tuberculin-positive in 1944, but in 70 of 269 who were tuberculin-negative reactors at that time. Twenty-seven of those who developed local lesions had not been tuberculin tested in 1944. Thus, it is possible that among these there were some who had already turned tuberculin-positive in the normal course of events by the time they received the typhoid inoculations. Of the 269 children who were tuberculin-negative in 1944, 14 developed positive tuberculin reactions by 1946 without the development of lesions. In 3 of these, exposure to pulmonary tuberculosis within the home or the development of idiopathic pleurisy could be traced.

Erythrocyte sedimentation rates were performed on the involved children as well as on those who were tuberculin-negative, and no decisive differences could be observed.

*Roentgenographic findings:* Chest films were obtained at three- to four-month intervals of 101 of the 102 children involved. Pathologic findings were observed in 20 of these. These pathologic findings were of a great variety: one child had miliary tuberculosis; 4 children, small foci in the pulmonary lung fields; 3 children, more or less ill-defined shadows in the pulmonary fields and 3 children had round shadows in the same areas. Two children had calcified foci in the lung parenchyma, and one of them had hilar calcifications. Two children had round, ill-defined shadows in their lung fields, but these were children with definite family histories of pulmonary tuberculosis. Eleven children showed evidence of pleurisy.

In contrast, chest roentgenograms were obtained of 57 children who were either tuberculin-negative or were not tuberculin tested in 1944, were vaccinated but had no local lesions in 1946, but who subsequently became tuberculin-positive late in 1946. Of these 57 children, one was a child with miliary tuberculosis whose mother was suffering from open pulmonary tuberculosis, 9 had calcified pulmonary shadows, 3 had fresh pulmonary infiltrates, and 5 showed evidence of pleurisy.

Chest roentgenograms were also obtained of 68 children who were tuberculin-positive, but who had not had any contact with the program of typhoid vaccination. Seven of these children showed pulmonary calcifications, one had small fresh infiltrative shadows, and one showed evidence of pleurisy.

In contrast to this, chest films were obtained of 106 nonreactors to tuberculin. Only one was found to have an ill-defined, hazy shadow in the right lower lung field, which disappeared two months later. The remainder showed no evidence of pathologic changes.

*Bacteriologic studies:* Cultures were taken of either sputum or pharyngeal and laryngeal secretions from 99 children who had developed local lesions. These studies were performed early in 1947, late in 1947, again in 1948 and 1949. Of these 99 children, 5 were found to have cultures positive for tubercle bacilli. Four of these 5 children showed abnormal shadows on the chest roentgenogram.

*Bone and joint tuberculosis:* Of the group of 102 children, 3 developed lesions of the bone and joints. One of these lesions was in the left first metatarsal bone, and local aspiration showed the presence of tubercle bacilli. The two other

lesions, which were negative for tubercle bacilli on culture showed an involvement of the dorsal spine and cranial bones, respectively. Two of the children also had pulmonary involvement as demonstrated by roentgenography.

From the above findings, no definite conclusion can be reached whether there was any connection between the bone and joint tuberculosis and the extirpation of the axillary lymph node involvement.

*Pathologic Findings*

Local cutaneous foci of 17 patients and the axillary lymph nodes of 45 patients were excised four and one-half months to two and one-half years after the typhoid vaccination and represent the basis for the subsequent discussion. The material was fixed in 10 per cent formalin solution, was embedded in celloidin or paraffin, and was stained with both hematoxylin and eosin as well as acid-fast stain. Van Gieson stains were used in several of the sections.

The pathologic findings can be presented in three categories, namely, those seen during the first six months after the injection of typhoid vaccine, those seen seven months to two years after the inoculation, and those observed after two years.

*Axillary lymph nodes excised six months after the typhoid inoculation:* Eight axillary lymph nodes were studied in this group of nodes excised six months after inoculation. These lymph nodes were involved by a single or multiple foci of caseous necrosis, many of which were found just beneath the capsule and which varied somewhat in size. At the periphery of these caseous foci were collections of parenchymal cells, plasma cells, polymorphonuclear leukocytes, and occasional epithelioid cells. Langhans' giant cells were not present. There were cellular infiltrations outside the capsule of lymph node, and these consisted of monocytes and plasma cells. There was some engorgement of perifocal capillaries, and occasional collections of perifocal eosinophilic polymorphonuclear leukocytes were seen. The lymphatic vessels in the vicinity of these foci were dilated and showed evidence of reticulo-endothelial hyperplasia. Early evidence of calcification of the caseous focus was noted in only one case.

*Axillary lymph nodes excised seven months to two years after the typhoid inoculation:* The axillary lymph nodes which were examined more than seven months after the inoculation of typhoid vaccine showed areas of caseous necrosis. In contrast to the foci seen in the earlier stage, the areas of necrosis were surrounded by narrow zones of epithelioid cells and monocytes which were much thinner than those observed in earlier stages. Beyond these, the formation of hyaline connective tissue and the production of a fibrous capsule were seen in many of the patients observed after the seventh month. In a number of cases, calcification of the central zones of caseation was observed. Frequently this calcification was seen before the formation of an actual fibrous capsule.

*Axillary lymph nodes excised after two years and after following the typhoid inoculation:* This group comprises 7 cases of axillary lymph node sections, 3 of which represented recurrent operative procedures. In summary, the main pathologic alterations of these lymph nodes showed extensive central calcification of the caseous foci. Several of the nodes in this group showed advanced healing

changes in terms of hyalinization of caseous and epithelioid cell foci, but at least one lymph node in this group failed to show any specific alteration of tuberculosis at all.

Two cases studied histologically were considered to be of the reinfection type. Several histologic sections from these patients failed to show any specific tuberculous involvement of the lymph nodes histologically, except in one section, in which a few focal collections of epithelioid Langhans' giant cells were seen within lymph node sinuses. These lymph nodes, however, showed evidence of extensive reticulo-endothelial hyperplasia. A portion of muscle taken from one of these patients showed the presence of epithelioid giant-cell granulomata compatible with tuberculosis.

It must be noted that, in instances of removal of several portions of axillary lymph nodes, the histologic picture was frequently not identical. In many of the nodes the picture was that of an epithelioid giant-cell granuloma with caseation, whereas other nodes showed largely reticulo-endothelial hyperplasia.

*Histologic picture of the cutaneous foci:* In 17 cases, local biopsies of the skin and subcutaneous tissue were obtained and showed the following changes. In most instances the skin was ulcerated by the time that excision was performed and the ulceration was lined by necrotic debris and pyogenic membrane, which in turn was surrounded by a narrow zone of tuberculous granulation tissue which contained Langhans' giant cells. The underlying subcutaneous zones showed extensive areas of scarring, with some dilatation of the local lymphatic channels. There was a moderate degree of perifocal, frequently perivascular, infiltration by lymphocytes and polymorphonuclear leukocytes.

*Bacteriologic findings:* The histologic preparations of both axillary lymph nodes and cutaneous foci were subjected to Ziehl-Neelsen staining, but the presence of bacilli could be recognized in only 3 cases. In addition, tubercle bacilli were found for cultivation in the skin lesions in 6 cases, in pus from the skin lesions in 7 cases, and in the axillary lymph nodes in 10 cases. This is in addition to the already mentioned aspiration of tubercle bacilli in one case of osseous tuberculosis, as well as the presence of a sputum positive for acid-fast bacilli in 5 of the cases of vaccinated reactors.

## DISCUSSION

Vaccination of 631 school children at the Dojo Primary School in Hyogo Prefecture resulted in local reactions at the site of inoculation as well as axillary adenopathy in 102 children. The course of the local and axillary indurations suggested tuberculous origin of these reactions. This was substantiated by the large number of positive tuberculin reactors in the group, compared to a previous or control group not similarly vaccinated, as well as the histologic picture of the excised lesions.

A number of children developed systemic tuberculosis, both of a pulmonary, pleural, and bone and joint variety, but it is difficult to prove whether these cases resulted from the above inoculation or whether they were related to the general prevalence of the disease in the population.

The pathologic findings in the skin lesions showed typical tuberculous ulcerations with tuberculous granulation tissue and surrounding scar formation. The axillary nodes were of interest in that the picture was somewhat different at early, intermediate, and late time intervals following inoculation.

Tubercle bacilli were found on Ziehl-Neelsen stain in 3 of the histologic preparations, but no other local evidence of tubercle bacilli could be proved. However, of the group involved, 5 patients developed sputum or nasopharyngeal secretions positive for *M. tuberculosis* following the course of vaccination.

The mechanism of the above experience is not clear at this time. Despite the fact that one of the persons administering the typhoid vaccine was subsequently found to have open chronic pulmonary tuberculosis, there was not sufficient correlation between the children who reacted and who were inoculated by this person to suggest that this was the only or even possible source of contamination. However, it is the writers' impression that there was a relationship between the typhoid vaccination and the introduction of tubercle bacilli which was based on the incidence of skin and lymph node tuberculosis in those exposed to the vaccine, compared to those not so inoculated. The exact mechanism of transmission, however, was not determined.

There appears to be evidence from the lymph node examinations in the present study that there is no relationship between the primary and secondary stages, as described by Ranke. The fallacy with Ranke's study is that it is based on the study of lymph nodes in autopsy material. According to Ranke, the primary complex is the first stage of tuberculosis which is characterized by draining of the primary focus into the regional lymph nodes. This occurs in a person previously uninfected by tubercle bacilli. Following this, there is a dissemination of tubercle bacilli through the blood stream, with resultant tuberculous foci in the different viscera. This Ranke designated as the second stage, and it occurs in a hypersensitive person.

The findings in the present study show that there is no relationship between the first and second stages and that they are both part of the pathologic process. What Ranke placed in two stages are in reality two phases of the same process. What Ranke classified as the primary stage is the healing phase of the lymph node tuberculosis, whereas the secondary stage is the active progressive phase of the lymph node tuberculosis.

The fact that Ranke's second stage—a dangerous period—promptly appears without passing through the primary stage should serve as a warning to clinicians.

It is of interest that almost all of the axillary lymph nodes in this study showed healing tendencies seven months after the inoculation. The primary foci of the skin, on the other hand, showed little tendency toward healing and thus remained in a stage of progression. None showed evidence of calcification.

## SUMMARY

A 1946 episode is described, in which tuberculosis of the skin and regional lymph nodes developed following inoculation with typhoid vaccine. This occurred in 102 of 631 primary school children at the Dojo Primary School in

Hyogo Prefecture. The lesions occurred primarily at the site of injection and became apparent one to six months after inoculation. Tubercle bacilli were identified in 29 cases, and histologic manifestations of tuberculosis were noted in 62 cases.

SUMARIO

*Observaciones acerca de una Epidemia de Tuberculosis Cutánea y Linfática Consecutivamente al Uso de Vacuna Antitifoidea*

Describese la aparición de tuberculosis de la piel y de los ganglios linfáticos regionales a continuación de la inoculación de vacuna antitifoidea. Esto sucedió en 102 de 631 alumnos de la escuela primaria de Dojo en la Prefectura de Hiogo, Japón. Las lesiones ocurrieron principalmente en el sitio de la inyección y se volvieron evidentes de uno a seis meses después de la inoculación. En 29 casos se identificaron bacilos tuberculosos y en 62 casos se observaron cuadros histológicos de tuberculosis.

RESUME

*Observations sur une épidémie de tuberculose de la peau et des ganglions lymphatiques après emploi de vaccin antityphique*

Description de cas de tuberculose de la peau et des ganglions lymphatiques apparus après vaccination antityphique. Ces faits se sont produits chez 102 enfants sur 631 écoliers de l'école primaire de Dojo, préfecture de Hyogo. Les lésions se sont manifestées au niveau de l'injection, elles sont devenues visibles entre un mois et six mois après l'inoculation. Les bacilles tuberculeux ont été isolés dans 29 cas; les lésions histologiques ont été observées dans 62 cas.

# OPERATIVE AND PATHOLOGIC FINDINGS IN TWENTY-FOUR PATIENTS WITH SYNDROME OF IDIOPATHIC PLEURISY WITH EFFUSION, PRESUMABLY TUBERCULOUS[1,2]

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## INTRODUCTION

Effusion into the pleural cavity constitutes a manifestation of a variety of diseases (1). In a great many instances the cause of the fluid collection can be determined. There remains, however, a significant number of cases of pleural effusion for which no cause can be identified. These cases have their peak incidence between the ages of fifteen and thirty years (2). Tuberculosis is said to be the cause of 80 to 90 per cent of these effusions (3), but all too often no proof of this disease can be found even with careful study. It seems rather drastic to many physicians to prescribe a long term of bed rest and antituberculous chemotherapy for a young person with a pleural effusion and no demonstrable evidence of tuberculosis. Nevertheless, in Roper and Waring's recent series from Fitzsimons Army Hospital, 66 per cent of the patients with simple pleurisy with effusion manifested active tuberculosis within five years of the effusion (4).

There is a paucity of information in the literature on the actual pathology of the pleura and underlying lung during an attack of pleurisy with effusion. Fitzsimons Army Hospital admits 100 to 125 patients with pleurisy with effusion every year, and the great majority of them are between eighteen and twenty-five years of age (5). The routine plan of therapy for these patients is essentially that given for readily resolving minimal pulmonary tuberculosis, i.e., twelve months of isoniazid-streptomycin or streptomycin-PAS. This therapy includes six months of fairly complete bed rest and six months of graduated physical activity. The program largely stemmed from Roper and Waring's findings and the presumption of a minimal tuberculous lesion. On this treatment program, the majority of the patients have shown nearly complete disappearance of the pleural fluid, with little or no residual blunting of the costovertebral angle on the chest roentgenogram. A few have shown marked residual pleural thickening and others have been left with intermediate degrees of pleural residuals. The size of the initial effusion has not appeared to be the principal determinant in the ultimate outcome.

The present report concerns the clinical, operative, and pathologic findings in a group of 24 patients who were explored surgically within a few months of the acute effusion. The findings shed light upon the pathogenesis of tuberculous

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pleurisy with effusion and are reported primarily from this point of view. Of secondary interest are the findings in some of the patients who had no evidence of tuberculosis.

## CLINICAL MATERIAL

Twenty-three of the patients upon whom this report is based were hospitalized on the Pulmonary Disease Service of Fitzsimons Army Hospital. One patient (*Case 3*) was on the Tuberculosis Service at Camp Carson Station Hospital, Colorado Springs, but was seen by one of the writers (W.W.S.). All of the patients were admitted because of pleural effusions for which tuberculosis was presumed to be the cause. In some instances reasonable bacteriologic evidence for this diagnosis was at hand before surgical intervention. It will be seen in table 1, however, that 3 of the patients who were subsequently found to be nontuberculous also had such bacteriologic "proof" originally.

All but one patient showed a positive tuberculin skin reaction and, in the nonreactor, acid-fast bacilli were reported to have been found in the pleural aspirate. The fluid was an exudate in every case in which specific gravity or protein was determined. In 2 instances, the fluid was bloody. For information on the pleural fluid, the principal reliance had to be placed on observations at smaller Army hospitals and dispensaries because thoracentesis frequently yielded no fluid by the time the patient had been transferred to Fitzsimons.

It is not the policy at Fitzsimons Army Hospital to explore all cases of idiopathic pleural effusion. It should be emphasized, therefore, that in every instance in the present series there was some aspect of the case which did not completely conform to the usual clinical picture of idiopathic exudative pleurisy. In 7 instances, exploration was prompted by the long-continued formation of fluid; in one, by the fear of tumor. Six patients were explored for the removal of parenchymal lesions which were presumed to be tuberculous and which had become evident after the effusion had partially cleared. The remaining 10 patients were explored for the purpose of decortication of a thick pleural peel.

In table 1 are summarized the essential clinical data as well as the available studies on the pleural fluids and the pathologic findings at the time of surgery. All but one of the patients were male. This is consistent with the hospital population. None of the patients had ever had tuberculosis before, and all were in relatively good health when the pleurisy began. The majority were engaged in vigorous duty in the field at the onset of illness.

It was surprising to discover that the surgical and pathologic findings divided the patients into two distinct groups, i.e., (*1*) those whose pleurisy was obviously tuberculous and in whom pulmonary tuberculosis was also found, and (*2*) those in whom the pleural peel was of a simple fibroid nature and in whom no evidence of active tuberculosis could be found pathologically. The findings of the two groups will be presented and discussed separately.

The majority of the patients were operated upon by the same surgeon (H.K.S.), and his observations were confirmed by several other experienced thoracic surgeons. In every instance but one (*Case 3*) a complete exploratory thoracotomy

TABLE 1

CLINICAL DATA AND AVAILABLE STUDIES ON PLEURAL FLUIDS AND PATHOLOGIC FINDINGS IN TWENTY-FOUR PATIENTS AT TIME OF SURGERY

| | Tuberculous (15 Cases) | Nontuberculous (9 Cases) |
|---|---|---|
| Age | | |
| Range | 20–49 years | 21–56 years |
| Mean | 25.3 years | 37.8 years |
| Race | | |
| White | 7 | 8 |
| Non-white | 9 | 1 |
| Positive skin tests | | |
| Tuberculin | 15 | 8 |
| Histoplasmin | 1 | 3 |
| Coccidioidin | 3 | 4 |
| Bacteriology (preoperative) | | |
| AFB in sputum or gastric washings | 5 | 2* |
| AFB in pleural fluid | 4 | 1† |
| Pleural fluid | | |
| Exudate | 4 | 7 |
| Transudate | 0 | 0 |
| Not studied | 8 | 1 |
| Obtained to time of surgery | 0 | 7 |
| Free fluid found at surgery | 0 | 5 |
| Fluid never obtained | 3 | 0 |
| Predominantly lymphocytes in fluid | 8 | 4 |
| Predominantly polymorphonuclears in fluid | 0 | 2 |
| Eosinophils in fluid | 0 | 2 |
| No cell count done | 7 | 1 |
| Operative findings | | |
| Pleural space preserved | 0 | 7 |
| Space obliterated by peel | 15 | 2‡ |
| Localized tuberculous nidus in lung | 12 | 0 |
| Lingula or middle lobe | 5 | |
| Apico-posterior segment, upper lobe | 4 | |
| Anterior segment, upper lobe | 1 | |
| Lower lobe (anterior basal segment) | 2 | |
| Suspected (preoperative roentgenogram) | 6 | |
| Other pathology in lung | | |
| Disseminated tuberculosis | 7 | 0 |
| Organized pneumonia | 0 | 4 |
| Bullous emphysema | 0 | 2 |
| Histoplasmosis | 0 | 1 |
| Lung normal | 0 | 2 |
| Pathologic findings | | |
| Tuberculosis of pleura | 15 | 0 |
| Tuberculosis of lung | 15 | 0 |
| Nonspecific fibrous pleuritis | 0 | 9 |
| Following inflammation | | 7 |
| Following hemorrhage | | 2 |
| AFB in lung lesion | 12 | 0 |
| AFB in pleural lesion | 11 | 0 |
| AFB in lung or pleural lesion | 14 | 0 |

* One was chromagen, and the other was a smear not confirmed by culture.

† Patient was tuberculin-negative. No acid-fast bacilli found in specimen.

‡ Post-hemorrhagic fibrothorax.

AFB = Acid-fast bacilli on microscopy or culture.

TABLE 2

SURGICAL AND PATHOLOGIC FINDINGS IN THE TUBERCULOSIS CASES

| Case<br>Age<br>Race<br>Sex | Pleura at Surgery | Pulmonary Nidus | Other Lung Nodules | Surgery Performed | Pathology and Bacteriology | Pathogenesis of Pleuritis |
|---|---|---|---|---|---|---|
| 1<br>24<br>Mexican<br>M | Obliterated 2–3 cm. peel | A-P segment LUL, contiguous with pleura | None | V and P DCTN; A-P segment LUL | Chronic granulomatous pleuritis; caseous TB LUL; no AFB (preoperative sputum positive for AFB × 3) | Rupture of caseous nodule LUL; no other palpable lesions in lung |
| 2<br>24<br>Mexican<br>M | Obliterated 0.5–2 cm. peel | RML contiguous with pleura | RUL<br>RML<br>RLL | V and P DCTN; wedge RML | Chronic granulomatous pleuritis; caseous TB, RML. Lung and pleura positive for AFB | Rupture of caseous nodule RML; RML lesion preceded pleurisy by 6 months (retrospect) |
| 5<br>22<br>W<br>M | Obliterated 1–3 cm. peel | RUL–RML contiguous with pleura | None | V and P DCTN; wedge RUL-RML | Chronic granulomatous pleuritis; caseous TB, RUL-RML. Lung and pleura positive for AFB | Rupture of caseous nodule RUL-RML; no other palpable lesions in lung |
| 7<br>24<br>Mexican<br>M | Obliterated 1–1.5 cm. peel | RML contiguous with pleura | None | Incomplete DCTN; wedge RML | Chronic granulomatous pleuritis; caseous TB, RML. Lung and pleura positive for AFB | Onset in POW camp. Rupture of RML lesion with partial healing before reaching hospital |
| 9<br>49<br>W<br>M | Obliterated 1–3 cm. peel | Lingula LUL contiguous with pleura | LUL<br>LLL | V and P DCTN; wedge lingula | Chronic granulomatous pleuritis; caseous TB, lingula. Pleura positive for AFB | Rupture of lingula lesion; rest of lung not densely adherent despite multiple TB nodules |

| | | | | | | |
|---|---|---|---|---|---|---|
| 12<br>20<br>N<br>M | Obliterated 2–3 cm. peel | Lingula LUL contiguous with pleura | LUL<br>LLL | V and P DCTN; wedges of LUL and LLL | Chronic granulomatous pleuritis; caseous TB, LUL, LLL. Lung and pleura positive for AFB | Multiple sizable nodules in lung but only lingula lesion densely adherent to the thick pleura |
| 13<br>22<br>W<br>M | Obliterated 1–3 cm. peel | None identified | Multiple RUL, RML, RLL | V and P DCTN; biopsy RUL | Chronic granulomatous pleuritis; caseous TB, RUL. Pleura positive for AFB | No single nidus identified; multinodular TB gave appearance of bronchogenic spread |
| 15<br>38<br>W<br>M | Obliterated 0.5–1.5 cm. peel | Posterior segment RUL contiguous with pleura | RUL<br>RML<br>RLL | V and P DCTN; wedge posterior segment RUL | Chronic granulomatous pleuritis; caseous TB, RUL. Lung and pleura positive for AFB | Rupture of RUL lesion; rest of lung not densely adherent to pleura despite multiple TB nodules |
| 17<br>27<br>Mexican<br>M | Obliterated 1–2 cm. peel | A-P segment LUL contiguous with pleura | None | V and P DCTN; segmental resection; A-P segment, LUL | Chronic granulomatous pleuritis; caseous TB, LUL. Lung positive for AFB | Rupture of LUL lesion; dense adherence of pleura to lung at this point; no other palpable lesions |
| 18<br>23<br>W<br>M | Obliterated 0.5–1 cm. peel | None identified | LUL<br>LLL (small) | V and P DCTN; A-P segment; LUL | Chronic granulomatous pleuritis; caseous TB, LUL. Lung lesion positive for AFB. Pleura healing | No definite nidus found; lung and pleura both healing and not very extensive amount of TB |
| 19<br>33<br>Japanese<br>F | Obliterated 1–3 cm. peel | Anterior basal segment RLL contiguous with pleura | RUL<br>RML<br>RLL | V and P DCTN; wedge RLL | Chronic granulomatous pleuritis; caseous TB, RLL. Lung and pleura positive for AFB | Rupture of RLL lesion which preceded pleurisy in retrospect; FA pulmonary TB found at surgery |

TABLE 2—*Continued*

| Case<br>Age<br>Race<br>Sex | Pleura at Surgery | Pulmonary Nidus | Other Lung Nodules | Surgery Performed | Pathology and Bacteriology | Pathogenesis of Pleuritis |
|---|---|---|---|---|---|---|
| 20<br>25<br>Hawaiian<br>M | Obliterated 1–4 cm. peel | None identified | Many LUL, LLL | V and P DCTN. Nodular A-P segment, LUL not resected | Chronic granulomatous pleuritis; multinodular TB in A-P segment LUL and LLL. Pleura positive for AFB | A-P segment LUL densely adherent to pleura and not decorticated; probable nidus but not so identified |
| 21<br>20<br>Mexican<br>M | Obliterated 0.2–0.7 cm. peel | Lingula LUL contiguous with pleura | A-P segment LUL | V and P DCTN; caseous pneumonia, lingula. Nodular TB LUL | Chronic granulomatous pleuritis; caseous pneumonia, lingula. Lung and pleura positive for AFB | A-P segment nodules seen on roentgenogram, but not attached to pleura; lingula intimately attached to thick pleura |
| 22<br>28<br>W<br>M | Obliterated 1–2 cm. peel | Posterior segment RUL contiguous pleura | None | V and P DCTN; wedge posterior segment RUL | Chronic granulomatous pleuritis; caseous TB, RUL. Lung and pleura positive for AFB | Caseous lesion in posterior segment RUL ruptured into adjacent pleural space |
| 23<br>25<br>W<br>M | Obliterated 1–1.5 cm. peel | Anterior segment RUL contiguous with pleura | Superior segment RLL | Incomplete DCTN; wedge RUL, superior segment RLL | Chronic granulomatous pleuritis; caseous TB, RUL, RLL. Lung and pleura positive for AFB | Caseous lesion in anterior segment RUL probably ruptured into pleural space; RLL lesion not adherent to pleura |

A-P: Apical posterior.
AFB: Acid-fast bacilli on microscopy or culture.
DCTN: Decortication.
V and P DCTN: Complete visceral and parietal decortication.
POW: Prisoner of war.
FA: Far advanced tuberculosis.

was performed. A less complete examination could have demonstrated the pleural pathology, but would have contributed little information on the pathogenesis of the disease. Furthermore, the nontuberculous cases would have remained an enigma.

## RESULTS

### *Tuberculous Effusions*

Fifteen of the 24 patients had clear pathologic evidence of tuberculosis in both the lung and pleura. The details of the gross and pathologic findings and an assessment of the pathogenesis of the effusion in each case are set forth in table 2.

*Pathogenesis:* In 12 of the 15 tuberculous patients, the operating surgeon was able to identity a caseous tuberculous focus in the lung contiguous with the diseased pleura. There was no evidence of the rupture of a mediastinal node in any case.

Characteristically, the pleural peel and the underlying lung were more intimately attached at one point than at others in such a manner that it was necessary to take an appreciable portion of lung tissue with the peel in order to accomplish the decortication. The disease of the pleura was more than just multiple adhesions between the visceral and parietal pleura. The pleural space was completely obliterated and could not be identified. The lung was surrounded by a fibrous sheet of varying thickness. Small pockets of liquid caseous material could be found by sectioning through the fibrous peel, but no free fluid was identified within the chest.

In 13 of the 15 cases, the thickness of the peel was greater than 1 cm. In 2 patients (*Cases 22* and *23* in table 2), the clearing of the pleural reaction had been satisfactory, as seen by roentgenograms, and the peel was found to be less than 1 cm. in thickness. The indication for exploration in these 2 patients was the resection of parenchymal nodules which had been identified roentgenographically. In both cases subpleural caseous tuberculosis was found contiguous with the pleura. In one of these instances, however, the lesion which had been identified by roentgenogram, and which was thought to be in the apico-posterior segment, proved to be deeper in the lung tissue. The nidus for the pleural tuberculosis in this case was a previously unrecognized area of caseous pneumonia in the lingula. The attachment between the thick fibrous pleura and the lingular lesion was quite intimate.

Seven of the 15 tuberculous patients showed multiple small foci of tuberculosis in all segments of the underlying lung. In 5 of these, the apparent nidus for the pleural contamination could also be identified in connection with the pleura. The extent of the tuberculosis in the 7 patients was assessed as being moderately to far advanced. In no instance had such extensive disease been demonstrated on roentgenograms of the chest.

In 3 of the 15 patients, no subpleural tuberculous focus was identified in connection with the diseased pleura at the time of surgical exploration. Two of these 3 patients were among the 7 with multiple foci of tuberculosis throughout the underlying lung. The third showed nodular caseous tuberculosis in the apico-posterior segment, but no contiguous subpleural nodules (*Case 18*).

*Pathology:* Pathologic study of the fibrous pleural peel showed the same aspect in all of these 15 cases (*see* figure 2*F*). Typical caseous tubercles were readily identifiable in the stained sections. In 12 of the 15 cases, acid-fast bacilli were demonstrated by appropriate staining of the caseous material which was found in small pockets within the fibrous peel.

The pathology of the pulmonary lesions was also typical for tuberculosis. The degree of activity varied considerably as judged by microscopic examination. In some instances the appearance of the lesion was that of caseous tuberculous pneumonia in a localized area, while in other cases the appearance was that of healing tuberculosis. Acid-fast bacilli were identified by appropriate staining methods in 11 of the 15 pulmonary lesions studied. Acid-fast bacilli were found in either the lung or pleura or both in all but one patient. The one patient whose pathologic study revealed no tubercle bacilli had had three sputum cultures positive for tubercle bacilli which were reported shortly after the operation. Eight of the 12 tuberculous foci were found on the anterior surface of the lung (*see* table 2 for the segments involved).

*Interval between onset of symptoms and operation:* The mean time elapsing from the onset of symptoms of exudative pleurisy to surgical exploration was eight and one-tenth months in this group with tuberculous lesions. Two patients were operated upon four months after the onset of symptoms; 3, five months after the onset. In 2 patients, thirteen months elapsed between time of onset of symptoms and the surgical exploration. One of these patients was in a Chinese prisoner-of-war camp when the symptoms began. The duration of preoperative chemotherapy also varied considerably. The mean was four and one-tenth months, and the therapy in every instance was isoniazid-streptomycin. The longest period of chemotherapy before surgery was ten months. One patient had had a proved episode of coccidioidomycosis a few months previously. He was operated upon, with a tentative diagnosis of coccidioidomycosis with effusion. It had been intended to give him isoniazid-streptomycin as a protective measure, but through an administrative error the drugs were not started preoperatively. In spite of this error, the course was smooth and the surgical results were good.

*Clinical results:* The clinical results were excellent in 12 of the 15 patients; in 2 the decortication was inadequate (*Cases 7* and *23*), and in one (*Case 21*) a staphylococcal empyema occurred when the underwater seal bottle was accidentally broken. In spite of the great variation in the duration of antituberculous chemotherapy before surgery, there were no complications which could be attributed to tuberculosis.

The following cases, representative of the tuberculous group, are presented:

*Case 2* (figure 1). A 25-year-old Mexican male gave a history of mild malaise and fever of two weeks' duration in August, 1952. In October, 1952, a pleuritic pain began in the right anterior chest. A chest roentgenogram (figure 1*A*) was interpreted as normal, but in retrospect an infiltrate was visible in the right mid-lung field. No pleural fluid was present at that time. The patient continued to complain of pleuritic pain but, in spite of this, was given a regular discharge from the Army because the chest roentgenogram was interpreted as normal.

In February, 1953, the patient experienced fever, cough, malaise, and a great accentua-

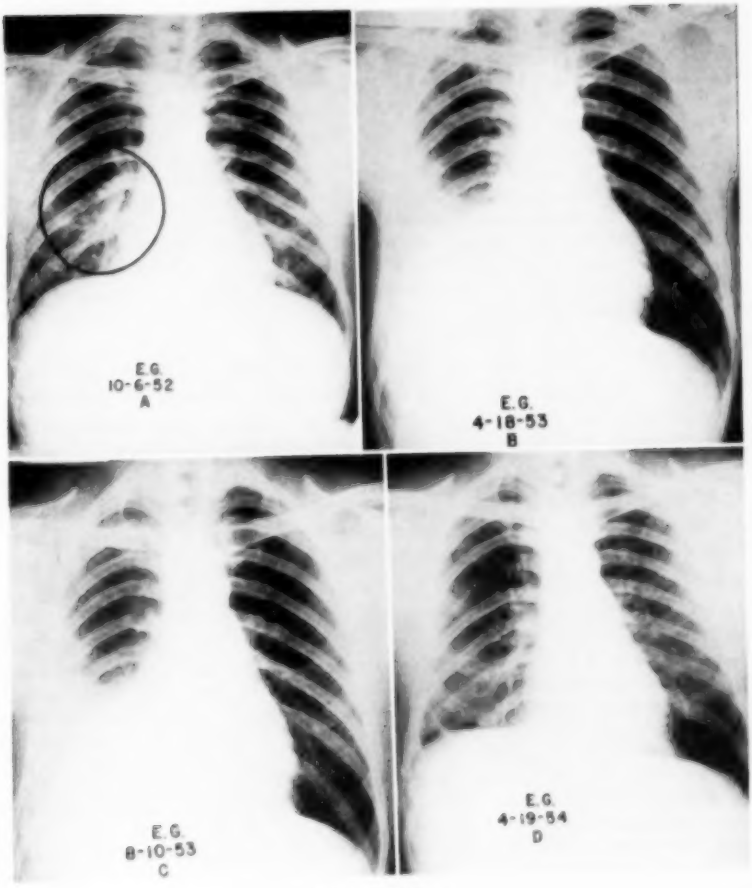


FIG. 1. *Case 2*

*A*. Chest roentgenogram taken in October, 1952, interpreted as normal, but later believed to show an infiltrate in right mid-lung field.

*B*. Chest roentgenogram taken in April, 1953.

*C*. Chest roentgenogram (October 10, 1953) obtained shortly before surgery.

*D*. Postoperative roentgenogram (January 9, 1954).

tion of the pain in the right chest. During this illness the patient lost considerable weight. He spent two weeks at bed rest and then attempted to return to his normal activities. He found that he suffered from weakness and easy fatigue. In March, 1953, a diagnosis of pleurisy with effusion was made by his physician, and he was given a course of penicillin therapy.

On April 17, 1953 (approximately ten weeks after the worsening of his illness in February, 1953), he was admitted as a veteran to Fitzsimons Army Hospital. At that time the physical signs were those of flatness to percussion of the right chest, distant breath sounds, and restriction of motion on the right. A chest roentgenogram obtained at that time is shown in

figure 1*B*. Thoracentesis yielded no fluid at the time of admission. This is not surprising since the pleuritis had probably already existed for ten weeks. The tuberculin reaction was positive. Sputum and gastric washings showed no tubercle bacilli on culture. The patient was put at almost complete bed rest and given isoniazid-streptomycin therapy.

Approximately three months later an exploratory thoracotomy was performed because of the fear of a neoplastic lesion in the pleura or lung. In figure 1*C* the chest roentgenogram is shown which was taken shortly before surgery.

At the time of the operation the pleural space was completely obliterated by a thick fibrous sheet. This pleural peel was stripped with reasonable ease except over the middle lobe area, where it was intimately attached to a caseous parenchymal lesion. In addition, multiple small tuberculous nodules were found in all segments of the right lung. These nodules had never been demonstrated roentgenographically. Sections of the fibrous pleura revealed caseous tubercles. Sections of the middle lobe lesion revealed caseous tuberculosis. Acid-fast bacilli were demonstrated in both the parenchymal and pleural lesions.

It is probable that in this case the thick granulomatous pleural peel was the end result of pleural effusion caused by the rupture of the middle lobe tuberculous lesion into the pleural space. The fluid had already been absorbed by the time the patient was admitted to the hospital. The relatively easy decortication may be related to the fact that surgery was performed only six months after the onset of the exudative pleurisy. The postoperative film is shown in figure 1*D*. The clinical as well as the roentgenographic results were excellent. The patient had received three months' chemotherapy preoperatively, and it was recommended that he receive eighteen to twenty-one months of chemotherapy postoperatively because of the great extent of the very active tuberculous process.

*Case 5* (figure 2). A 22-year-old white male was apparently in good health until June 23, 1953, when he noted sudden progressive dyspnea with fever, headache, and malaise. The chest roentgenogram obtained the next day is shown in figure 2*A*. Thoracentesis was performed, and approximately 1,500 cc. of a straw-colored serous fluid were removed. No studies were done on this fluid. On June 29, 1953, 1,000 cc. of straw-colored serous fluid were removed and revealed 1,200 leukocytes per cu. mm., 100 per cent of which were lymphocytes. A few acid-fast bacilli were seen on the smear of this fluid. The tuberculin reaction was positive. Cultures of sputum and gastric washings were negative for tubercle bacilli. The patient was started immediately on isoniazid-streptomycin therapy and was transferred to Fitzsimons Army Hospital. The effusion cleared rather readily, and no parenchymal lesion was demonstrated on standard roentgenograms. Thoracentesis at the time of admission to Fitzsimons yielded no fluid, in spite of an appreciable roentgenographic density, suggestive of either pleural thickening or fluid. Decortication of the right lung was recommended in November, 1953, for the purpose of removing the thick pleural peel from the right lung (figure 2*C*). The patient had received isoniazid-streptomycin for five months prior to surgery.

At operation the pleural space was completely obliterated by a thick, fibrous pleura which could be stripped with moderate ease except over the right middle lobe area, where it was found to be densely adherent to a caseous parenchymal focus. The macroscopic appearance of this peel is shown in figure 2*E*. Microscopically, the fibrous pleural peel was typically tuberculous in nature (figure 2*F*). Section of the pulmonary lesion showed caseous tuberculosis. Acid-fast bacilli were found in the pulmonary lesion and in the caseous material which occurred in small pockets in the thick fibrous pleural peel. The surgeon described the remainder of the right lung as normal to palpation. The postoperative roentgenogram is shown in figure 2*D* and reveals an excellent result.

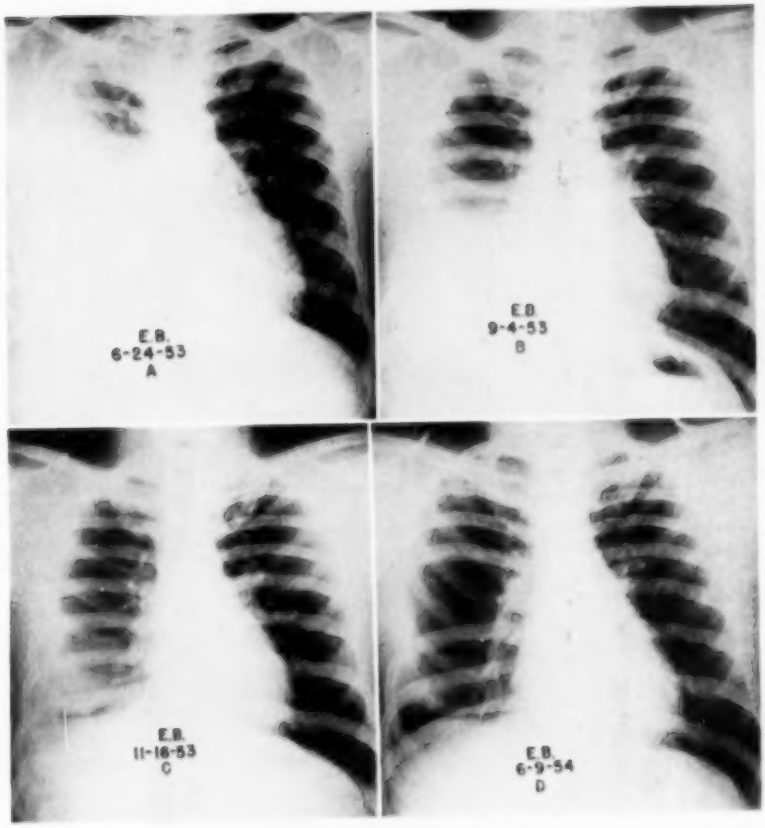


FIG. 2 (*A-D*). *Case 5*

*A*. Chest roentgenogram obtained on June 24, 1953.

*B* and *C*. Preoperative chest roentgenograms (September 4 and November 16, 1953).

*D*. Postoperative chest roentgenogram (June 9, 1954), showing excellent result of operation.

(The lesion in the right middle lobe was not indicated on the roentgenograms.)

Because of the considerably more limited nature of the tuberculosis and its greater tendency toward healing in this patient than in the patient of *Case 2*, a shorter period of postoperative chemotherapy was prescribed, i.e., ten months. The surgical findings in this case are shown in diagrammatic form in figure 3*A*.

### *Nontuberculous Effusions*

Nine of the 24 patients showed no evidence of tuberculosis. The significant data on these patients are contained in table 3. All of these patients had been

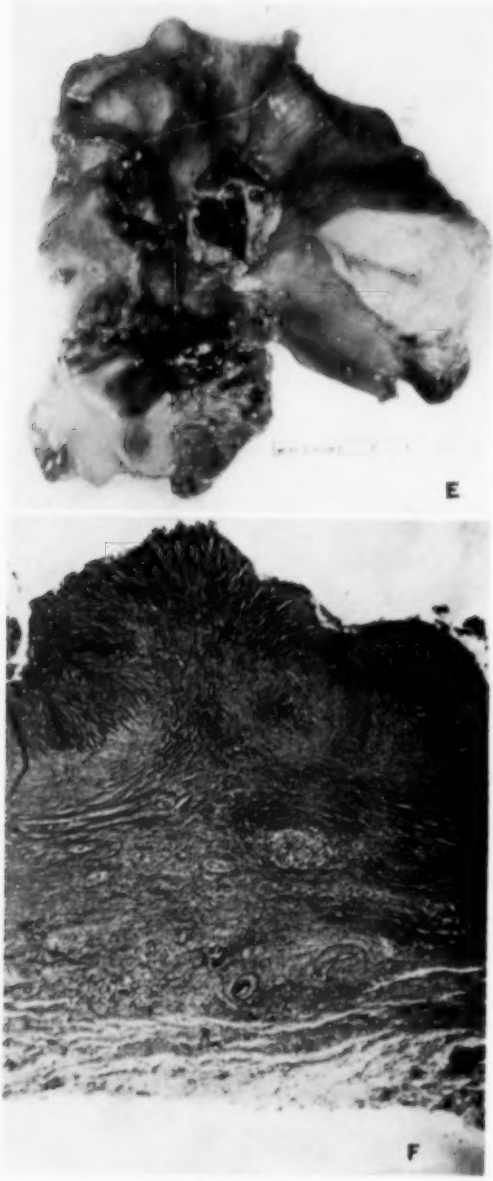


FIG. 2 (*E-F*), *Case 5*

*E*. Macroscopic appearance of peel stripped from pleural space.
*F*. Microscopic appearance of same peel.

TABLE 3

SURGICAL AND PATHOLOGIC FINDINGS IN THE NONTUBERCULOUS CASES

| Case<br>Age<br>Race<br>Sex | Gross Surgical Findings<br>Pathology of Pleura | Pulmonary Pathology | Pathogenesis of Pleuritis and Effusion |
|---|---|---|---|
| 3<br>33<br>N<br>M | Free pleural space with fluid; RLL small and covered by 0.2 cm. peel; nonspecific fibrous pleuritis | None found; inadequate exploration; no evidence of TB | Cause of pleural peel undetermined; continuous fluid formation for 24 months, probably due to trapping of RLL by fibrous pleural peel. |
| 4<br>56<br>W<br>M | Free pleural space with fluid; 0.2 cm. peel covering LLL, reducing it to ½ normal volume; nonspecific fibrous pleuritis | Multiple subpleural bullae; history at onset suggestive of spontaneous PNX; no evidence of TB | Fibrous pleural peel possibly result of fibrin in pleural space at time of spontaneous PNX; fluid formation on mechanical basis due to trapped LLL and inability of LUL to fill space. |
| 6<br>46<br>W<br>M | Free pleural space with fluid; LLL small and covered by 0.1–0.2 cm. peel; nonspecific fibrous pleuritis | Subpleural and hilar node foci of active histoplasmosis; no evidence of TB | No cause for pleural thickening and trapping of LLL found unless related to subpleural histoplasmosis; fluid formation on mechanical basis due to trapping of LLL. |
| 8<br>38<br>W<br>M | Free pleural space without fluid; lingula and LLL small and covered by 0.2–0.3 cm. peel; nonspecific fibrous pleuritis | Organizing pneumonitis A-P segment, LUL; bullous emphysema; no evidence of TB | Pleural peel may have resulted either from organizing pneumonitis of LUL or from spontaneous PNX due to emphysema. Fluid formation on mechanical basis due to trapping of LLL and lingula LUL |
| 10<br>54<br>W<br>M | Free pleural space with fluid; LLL very small and covered by 0.1–0.3 cm. peel; nonspecific fibrous pleuritis | Organizing pneumonitis A-P segment, LUL; no evidence of TB | Pleural peel possibly caused by patch of organizing pneumonitis in A-P segment LUL; continuous fluid formation on mechanical basis due to trapped LLL and inability of LUL to fill space. |
| 11<br>30<br>W<br>M | Free pleural space with fluid; RLL small, indurated and covered by 0.2 cm. peel; nonspecific fibrous pleuritis | Chronic organizing pneumonitis and bronchiectasis, basilar segments RLL; no evidence of TB | Definite chronic pneumonitis in basilar segments RLL probable cause of original pleuritis; fluid formation probably on mechanical basis due to trapping RLL. |

TABLE 3—*Continued*

| Case<br>Age<br>Race<br>Sex | Gross Surgical Findings<br>Pathology of Pleura | Pulmonary Pathology | Pathogenesis of Pleuritis and Effusion |
|---|---|---|---|
| 14<br>29<br>W<br>M | Free pleural space without fluid; RML and RLL small and covered by 0.3 cm. peel; nonspecific fibrous pleuritis | Organizing pneumonitis RUL; no evidence of TB | Pleural peel possibly caused by organizing pneumonia RUL; continued fluid formation due to trapping of RML and RLL and inability of RUL to fill resulting dead space. |
| 16<br>21<br>W<br>M | Obliterated pleural space; thick fibrous peel over whole lung; nonspecific fibrous tissue. | Lung normal; no evidence of TB; tuberculin reaction (PPD) was negative, but AFB had been reported in pleural fluid | Chest trauma plus bloody fluid make it likely that thick fibrous pleural peel was result of traumatic hemothorax. |
| 24<br>33<br>W<br>M | Obliterated pleural space; thick fibrous peel over whole lung; nonspecific fibrous tissue | Chronic organizing pneumonia RUL; no evidence of TB; lung bullae seen in opposite lung on roentgenogram | Initial fluid level plus bloody fluid plus bullae in left lung make strong case for spontaneous hemopneumothorax as the cause of the thick pleura over the whole lung. |

A-P: Apico-posterior.
PNX: Pneumothorax.
AFB: Acid-fast bacilli on microscopy or culture.

diagnosed as having idiopathic pleural effusion, presumably tuberculous, and were receiving treatment for tuberculosis.

Seven of the 9 patients were found to have a very thin fibrous peel compressing and distorting the lower lobe. In several instances the lingula or middle lobe was at least partially encased by the same peel. In contrast to the patients with tuberculosis, the pleural space was easily identifiable in all of these 7 patients, and in 5 instances 300 to 500 cc. of free pleural fluid were found at the time of surgical exploration. When the fibrous peel was removed from the lower part of the lung, the underlying lower lobe expanded readily to fill its normal space. This was true in all but one instance (*Case 11*), in which the basilar segments had to be resected because of cylindrical bronchiectasis and organizing pneumonia.

The underlying lung revealed no evidence of tuberculosis in any of the patients. In one (*Case 4*), subpleural bullae were found, and organizing pneumonia was present in 4 others. A subpleural focus of active histoplasmosis and a hilar node showing the same disease were found in another patient. The significance of this finding is not clear. In 2 instances no cause for the original formation of the thin

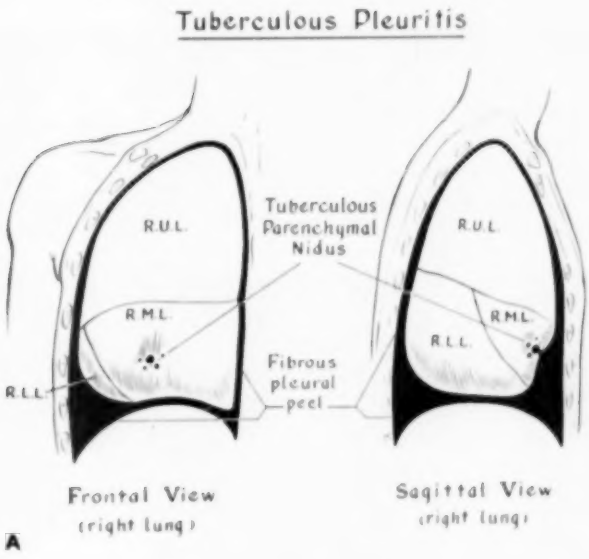


FIG. 3. Diagrammatic representation of the operative findings which characterized tuberculous and nontuberculous pleuritis. In *A* a subpleural tuberculous focus is shown in connection with the thick pleura. In *B* the trapping of the lower portion of the lung by a thin tough fibrous peel is shown. The resulting dead space is filled by fluid.

fibrous peel over the lower lobe could be assigned. The operative findings in these patients are shown diagrammatically in figure 3*B*.

The average duration of the pleural effusion before surgical exploration was eleven and three-tenths months. The patients had received an average of seven and seven-tenths months of chemotherapy before surgery.

A representative case is presented in detail:

*Case 4* (figure 4). A 56-year-old white male was in good health at the time of a routine chest roentgenogram on November 7, 1952 (figure 4*A*). This film appeared to be normal.

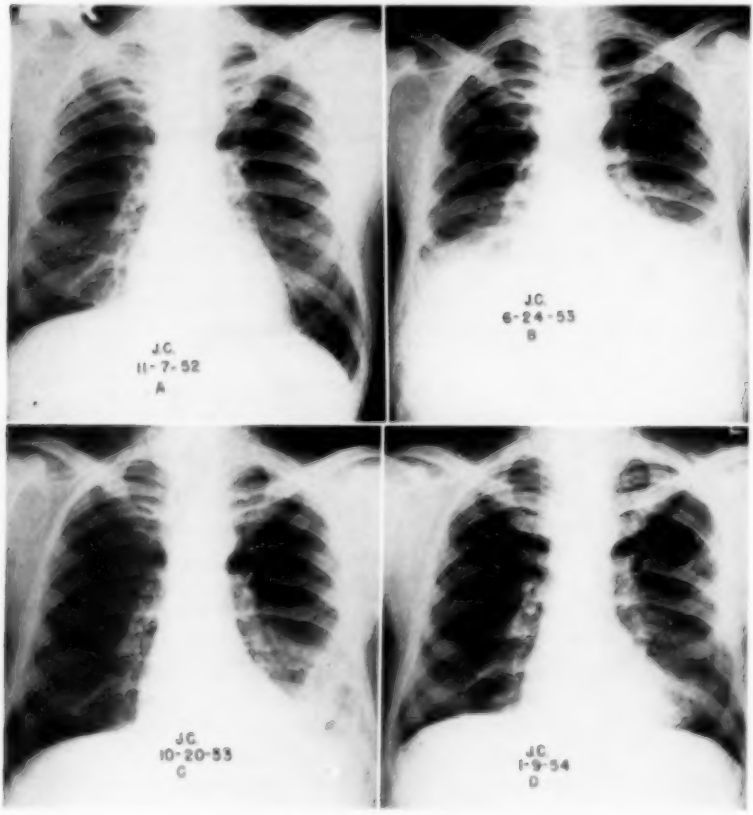


FIG. 4 (*A-D*). *Case 4*

*A*. Chest roentgenogram taken on November 7, 1952, interpreted as normal.

*B*. Chest roentgenogram obtained on June 24, 1953, after which a diagnosis of pleural effusion was made.

*C*. Preoperative chest roentgenogram (October 20, 1953).

*D*. Postoperative chest roentgenogram (January 9, 1954), showing little residual thickening and no fluid.

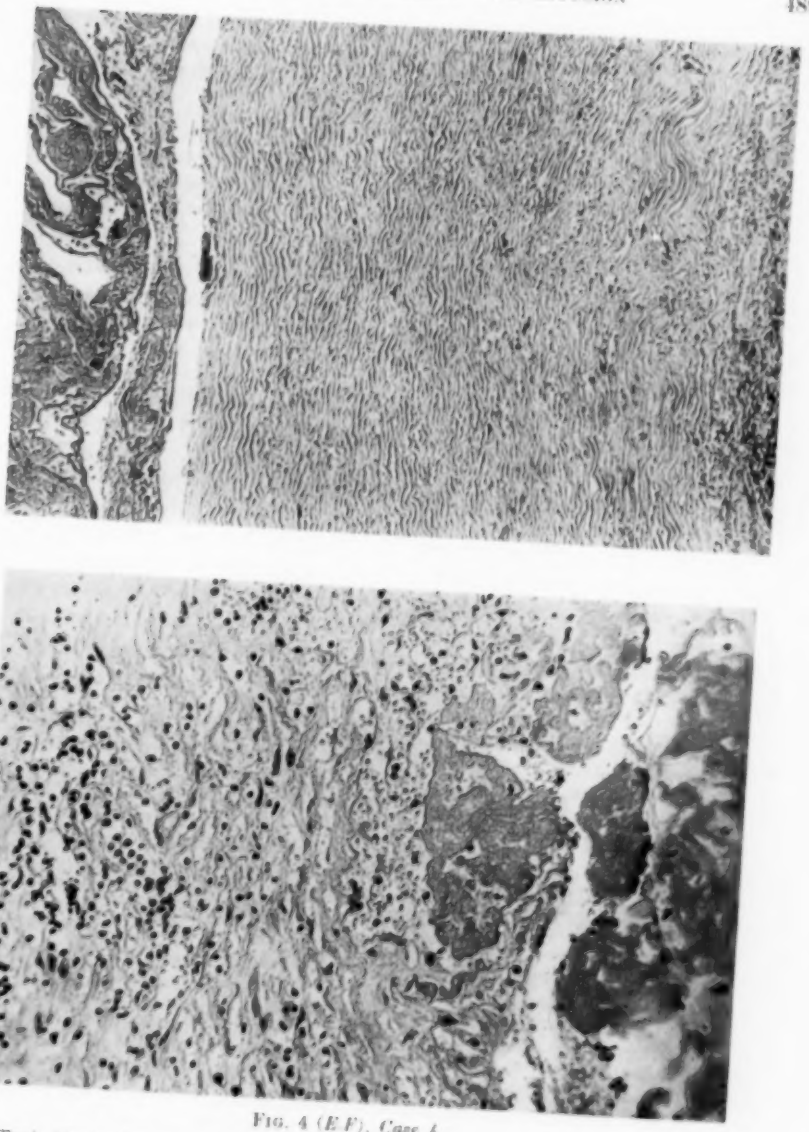

FIG. 4 (*E F*). *Case 4*

*E* (Top). Photomicrograph of section of pleural peel (low-power magnification).
*F* (Bottom). High-power magnification of same section.
The difference between nonspecific fibrous pleuritis and the granulomatous pleuritis shown in figure 2*F* is obvious at a glance.

Shortly thereafter, however, the patient suffered dyspnea and fatigue without other symptoms. No roentgenogram was made at that time and the symptoms subsided within ten days. In June, 1953, the patient noted the onset of left pleuritic pain, and a diagnosis of pleural effusion was first made roentgenographically (figure 4*B*). At that time 300 cc. of straw-colored fluid with the characteristic of an exudate were first obtained. Similar fluid was obtained repeatedly up to the time of surgery. Fluid reaccumulated rapidly to approximately the same point after each aspiration. The tuberculin skin reaction was positive. Culture and guinea pig inoculation of the pleural fluid and of the sputum and gastric washings revealed no tubercle bacilli. The preoperative roentgenogram is shown in figure 4*C*. At the time of surgical exploration, a free pleural space was encountered, but the lower lobe and lingula were seen to be shrunken, small, and encased by a thin fibrous visceral peel. The upper lobe was covered by a very slightly thickened pleura and apparently could not descend to occupy the dead space left by the shrunken lower lung. Straw-colored fluid occupied the dead space. Subpleural emphysematous blebs were readily detected in both lobes. No evidence of tuberculosis could be found.

The nature of the onset of the symptoms (dyspnea and fatigue), coupled with the finding of multiple subpleural blebs and generalized emphysema, suggested that an unrecognized spontaneous pneumothorax might have been associated with a small intrathoracic hemorrhage and might have caused the pleural fibrosis. The patient had received five months of rest with four months of isoniazid-streptomycin therapy preoperatively. The microscopic appearance of the pleural peel is shown in figures 4*E* and *F*. The fibrous nonspecific nature of the pleuritis is obvious; no granuloma could be found. The final diagnosis was chronic nonspecific pleuritis and bullous emphysema of the lung.

The remaining 2 patients in this group constituted a somewhat different problem both clinically and pathologically.

The first (*Case 18*) was a 21-year-old white male who was first hospitalized approximately two months after moderately severe, nonpenetrating trauma to the chest. Bloody fluid was aspirated on several occasions. At the time the patient was first seen at this hospital, the pleural reaction was extremely marked, as shown on the roentgenogram, and bloody fluid was still obtainable. The tuberculin skin reaction (0.02 mg. of PPD) was negative. The laboratory reported acid-fast bacilli in a smear of this bloody pleural fluid. For this reason the patient was considered possibly to have tuberculosis of the pleura. At the time of exploration the pleural peel grossly resembled that seen in tuberculous pleuritis in that it was thick, completely obliterating the pleural space. The decortication was easy and the peel was not bound to the lung at any point. Microscopic section revealed only fibrous tissue and no evidence of granulomata. The underlying lung was completely normal. The case, therefore, was considered to be one of traumatic hemothorax and resultant fibrothorax. This was the one patient who did not receive any chemotherapy for tuberculosis prior to exploration, but this was due to an administrative error. It had been the intent of the ward personnel to give the patient isoniazid-streptomycin.

The second of these patients (*Case 24*) was a 33-year-old white male who was first seen because of a history of dyspnea. The initial film revealed a fluid level, and a chest aspiration yielded bloody fluid. The findings at thoracotomy were exactly like those described in *Case 16* above. This patient likewise was believed to have had a spontaneous hemopneumothorax with a resultant fibrothorax, due to a rather large amount of blood in the thoracic cage.

## DISCUSSION

The literature on the subject of pleural effusion is voluminous, and no attempt will be made to review it completely. The majority of the papers approach the subject as a tuberculous manifestation, and several different types of phenomena are offered in evidence. Prominent among these are: the incidence of active pulmonary tuberculosis within the five years immediately following the effusion; the history of pleural pain in the course of pulmonary tuberculosis; the incidence of the demonstration of tubercle bacilli in the pleural fluid or in the gastric washings or sputum of patients with pleural effusion; and the frequency with which patients with idiopathic pleural effusion give a history of erythema nodosum within the preceding few months.

It has not been possible to find reports of surgical exploration of patients at the time of the acute pleuritis and, indeed, no recent reports of autopsied cases were encountered.

Laennec (6) first advanced the view in 1818 that pleurisy was simply a manifestation of tuberculosis. In 1883, Weigert (7) stated that a tuberculous lesion of the lung always underlay the granulomatous pleura, but he cited no specific cases. In 1886, Kelsch and Vaillard (8) reported fourteen autopsied cases of acute pleurisy with effusion, in eleven of which they found a definite pulmonary focus. Their interpretation was that the parenchymal focus was secondary to the pleural disease. Also, in 1886, Landouzy (9) reported on the autopsies of two patients with idiopathic pleurisy with effusion who had died suddenly following thoracentesis. In each instance he found a tuberculous lesion in the underlying lung tissue and believed that pleurisy was simply a manifestation of tuberculosis of the lung.

Landouzy made the point that his patients were both in vigorous health prior to the acute pleuritis and that there had been no suspicion of tuberculosis prior to the autopsy. Miller (10) reported on the pathology of tuberculous pleurisy, but made no clear distinction between patients with primary idiopathic pleurisy and those with known tuberculosis who had subsequently developed pleurisy. It is generally agreed among clinicians that such a distinction is necessary because the prognosis of a tuberculous patient who develops a pleurisy with effusion is rather serious, whereas the prognosis of a previously well patient who develops idiopathic pleural effusion is considerably better (2, 11).

Strandgaard (3) noted that 33 per cent of patients in whom a parenchymal lesion could be demonstrated roentgenographically subsequently developed pulmonary tuberculosis. When no such lesion was demonstrated, the tuberculous morbidity was only 10 per cent. Jacobaeus (12) was unable by means of the thoracoscope to distinguish the appearance of the pleura in idiopathic exudative pleurisy from that in proved pleural tuberculosis secondary to pre-existing pulmonary tuberculosis. He noted that in both conditions the pleura was hyperemic, studded with tubercles, and covered by fibrin.

The principal evidence for the tuberculous nature of primary idiopathic pleurisy with effusion remains clinical in nature. Allard and Köster (2) first

reported in 1911 that, of 514 patients with undiagnosed pleurisy with effusion, 47 per cent subsequently developed tuberculosis of the lung. Many writers since that time have found the incidence of pulmonary tuberculosis to vary between 5 and 66 per cent following idiopathic pleurisy with effusion. This subject was well summarized by Frostad in 1951 (13). More recently Roper and Waring (4) have reported that 66 per cent of their 141 cases of exudative pleurisy among Army personnel subsequently developed active pulmonary tuberculosis. The majority of reports of large series of patients with effusion have shown that approximately 23 per cent have subsequently developed pulmonary tuberculosis.

Wallgren (14) noted the high incidence of positive tuberculin reactors among the patients with pleurisy with effusion in contrast to the general population. He also postulated that the development of pleurisy was a manifestation of a marked hypersensitivity to tuberculin rather than a specific infection of the pleura. Arborelius (15) noted that exudative pleurisy developed in 30 per cent of Swedish Army draftees who developed clinically recognized primary tuberculosis while under his observation.

The incidence of the isolation of *M. tuberculosis* from the gastric washings, the sputum, or the pleural fluid has been commented upon by a number of writers. No one has ever found bacteriologic proof of tuberculosis in all of his patients, but all clinicians have noted a considerable incidence of cultures positive for tubercle bacilli in patients with exudative pleurisy.

Bezançon and Weil (16) have advanced an interesting view on idiopathic pleurisy with effusion. They noted that, on the tuberculosis service of a rather large hospital, they saw only a very occasional case of pleural effusion; whereas, in the comparably large general medical service of the same hospital, acute pleurisy with effusion was quite common. They agreed that the subsequent development of pulmonary tuberculosis was common following idiopathic pleurisy with effusion. They postulated that pleurisy was simply an indication of a predisposition to the development of tuberculosis and not a manifestation of tuberculosis itself, since so few cases first appeared on the tuberculosis service. Bezançon and Weil (17) reported the autopsy of two patients who died during a thoracentesis for a simple pleural effusion. In each patient they found a caseous focus in the lung just beneath the pleura. In one of these cases there were two inspissated cavities, 1 cm. in diameter, one of which showed definite connection with the pleura. They conceded that these two patients followed Landouzy's concept (9), but believed that the subpleural parenchymal tuberculosis was an unusual cause of pleurisy with effusion.

Paterson (18), in 1917, laid the groundwork for the current concept of idiopathic pleurisy with effusion. He demonstrated that tuberculin-sensitive guinea pigs showed a vigorous reaction of the pleura with a rather large effusion when tubercle bacilli were placed in the pleural cavity. Tuberculin-negative guinea pigs showed no such effusion, but developed disseminated tuberculosis. It is well accepted that exudative pleurisy in man occurs only in tuberculin skin reactors. There is considerably less agreement on the route by which the organisms or their products reach the pleura.

The most generally supported view on the manner by which the tubercle bacillus or its products reach the pleura is via lymphatic drainage of a subpleural focus. Miller (19) believed that the outer 1 to 2 mm. of parenchymal tissue were drained toward the pleura and thought this to be the means of pleural contamination. However, Simer (20) has shown that the lymphatic drainage of the lung is all toward the hilum and that the lymphatic drainage of the pleura is both to the hilar nodes through the pulmonary interlobular septa and to the para-aortic and para-sternal nodes. Medlar (21) stated that he has been impressed by the few cases of minimal tuberculosis which have any significant pleural symphysis except directly over the local lesion. For these reasons it seems unlikely that bacilli from an ordinary minimal parenchymal focus reach the pleura in sufficient numbers to give rise to a massive effusion and generalized pleural symphysis simply by proximity to the pleura. Offrem (22) and Bonilla (23) favor the view that pleurisy is a manifestation of a hematogenous dissemination of tuberculosis in the post-primary phase. Erwin (24) has drawn attention to the hilar adenitis that is common with primary tuberculous infections and believes that the contamination of the pleural space may occur by means of a rupture of a tuberculous hilar lymph node. He presented no direct evidence, however, and only a few such cases have ever been reported.

From the finding of a contiguous subpleural focus in 12 of the 15 tuberculous patients in the present study, the writers would like to endorse the following explanation for tuberculous pleurisy with effusion which was originally proposed by Le Damany (31) in 1903:

> In the post-primary phase of tuberculosis, a peripheral lesion occasionally ruptures into the pleural cavity and spills its caseous contents (*see* figure 3.4). In the tuberculin-sensitive subject the contaminated caseous material excites a vigorous reaction of the serous pleura with a great outpouring of an exudate which frequently contains a rather high proportion of polymorphonuclear neutrophilic leukocytes during the very early phase. The tubercle bacilli contained in the caseous material set up an actual tuberculous infection in the pleura (which was identified without question in all 15 of the tuberculous patients). The dilution of these organisms by the great outpouring of fluid and the phagocytosis of the bacilli make the organisms difficult to isolate. Eberle (25) has shown that the ability to demonstrate tubercle bacilli in pleural fluid is greatly improved by the concentration of larger amounts of the fluid.

The great incidence of exudative pleurisy in the age group of eighteen to twenty-five and among recently drafted soldiers (4, 5, 15) suggests that exudative pleurisy is part of the primary infection. The positive tuberculin reaction places it in what is usually called the post-primary phase.

The clinical course which the majority of patients with idiopathic pleurisy with effusion follow is precisely that demonstrated by Paterson (18) in tuberculin-sensitive guinea pigs. He showed that the initial reaction was the formation of a great deal of serous exudate and that this subsequently was reabsorbed by the body in the majority of instances. In some the pleural effusion was bloody, and death occurred during the acute period of the effusion in a few instances. In the majority, however, fluid was reabsorbed, and the guinea pigs lived ten weeks or

more. Some of these pigs showed fibrous peels of granulomatous nature. It is not surprising, therefore, that, when a small tuberculous focus ruptures into the pleural space of a tuberculin-reactive human, a vigorous outpouring of serous exudate takes place and that the subject subsequently recovers, reabsorbs the fluid, and returns to an apparent state of health in the majority of instances. Bloody pleural effusion is uncommon with tuberculosis and, in general, is associated with the rather severe pleural reaction. A few of Paterson's tuberculin-sensitive guinea pigs developed generalized tuberculosis. This is also seen in an occasional case of idiopathic pleural effusion in man and is probably the result of the entry of tubercle bacilli into the blood stream through the pleural lymphatics.

The work of Burke (26) on the pathogenesis of extrapulmonary tuberculosis is of great interest in this connection. He has shown that fine carbon particles and tubercle bacilli are picked up by the lymphatics of the pleura and deposited in the paravertebral, para-aortic, and parasternal lymph nodes. He has pointed out that these are the sites for the common occurrence of vertebral and chest wall tuberculosis. These nodes also connect with the thoracic duct and thereby give a portal of entry for tubercle bacilli into the blood stream. The greater incidence of Pott's disease and chest wall abscesses following pleural effusion than that following simple pulmonary tuberculosis is quite well recognized. In the tuberculin-negative guinea pigs, Paterson (18) showed that the guinea pigs quite regularly died of disseminated tuberculosis.

Seven of the 15 tuberculous patients in the present study showed multinodular tuberculosis in all segments of the lung. This would have warranted a classification of moderately to far advanced tuberculosis if it had been demonstrable roentgenographically. This rather widely disseminated tuberculosis could have been due to a bronchial dissemination. It seems more likely that it was infection in the lymphatics which drain the pleural surface and approach the hilum by way of the interlobular septa. Such lymphatics have been demonstrated by Miller (19), Simer (20), and others. In either event, the multinodular tuberculosis would lead almost beyond question to rather generalized pulmonary fibrosis. Carroll and associates (27) have commented upon an interlobular fibrosis which characterizes tuberculous fibrothorax. The present writers postulate that the dissemination of tuberculosis through the pulmonary lymphatics may account for this type of fibrosis. Certainly the stage was set for the formation of disseminated pulmonary fibrosis in the 7 patients who showed multiple tuberculous nodules throughout the lung.

In 3 of the tuberculous patients, no definite subpleural parenchymal focus could be identified as the nidus for the pleural infection. Two of the 3 showed multiple small tuberculous nodules throughout the lung. In one (*Case 18*) there were tuberculous nodules in the left upper lobe, but no lesion which appeared to be the nidus for the pleurisy. It is possible that a small tuberculous focus had ruptured into the pleural cavity deep within a pleural fissure and was therefore not identified at the time of surgical decortication.

The duration of therapy prescribed for idiopathic pleural effusion varies greatly

in the many reports in the literature. Mitchell (28) and Kallner (29) recommend rest therapy during the stage of the acute toxicity and a short period of convalescence thereafter before the patient returns to work. At the other extreme is the Army-Navy-Veterans Administration cooperative study regimen (30) which consists of eight to twelve months of multiple-drug therapy in conjunction with sanatorium care for every patient with idiopathic pleural effusion.

Among the 15 tuberculous patients in the present study, there were some who would probably have been quite well off if they had received bed rest and chemotherapy during the stage of acute toxicity because the tuberculous lesion was of a minor nature. Several other patients who did not appear any more seriously ill than the aforementioned group should quite probably have received at least an eighteen-month course of sanatorium care and chemotherapy because of the presence of moderately to far advanced pulmonary tuberculosis. In no instance was this degree of pulmonary involvement detected by roentgenography. One of the greatest benefits of surgical exploration of these patients was that the physicians in charge of the patients were able to prescribe therapy in accordance with the extent of the tuberculosis which was found surgically.

Another interesting aspect of the tuberculous nature of pleural effusion is the fact that the subsequent tuberculosis not infrequently appears either bilaterally or in the contralateral lung. Roper and Waring (4) reported that, in 57 patients who later developed pulmonary tuberculosis, 33 of the lesions were in the homolateral lung, 23 in the contralateral lung, and one in both lungs. Either the pulmonary seeding must be fairly widespread at the time of the original infection or the contralateral lung becomes infected by hematogenous spread. The caseous focus on the involved side often escapes detection, and certainly one might also be present in the contralateral lung.

One reason for the short period of therapy prescribed for pleurisy by some physicians is the observation that the rate of subsequent tuberculosis is not affected by sanatorium care (28, 29). It must be remembered, however, that only the more seriously ill patients are usually sent to a sanatorium and that the patients with the mildest disease receive only short periods of rest. The great variation in the extent of the pulmonary disease in the 15 patients of the present study affords an explanation for the greater rate of occurrence of tuberculosis among the patients who have rather widespread pulmonary tuberculosis.

Some small tuberculous foci might be detected by the routine use of planigraphy in cases of idiopathic pleural effusion. In figure 5 may be seen the roentgenograms of a patient who had not yet been operated upon but in whom it was possible to demonstrate by planigraphy a nodular lesion in the anterior basilar segment of the left lower lobe. The first film (*A*) shows a moderate left pleural effusion which disappeared in approximately six weeks. On the film of May 10, 1954 (*B*) a faint density can be seen in the region of the sixth anterior rib. This area is better seen in the magnified view (*C*) and was interpreted as representing a slight thickening of the pleura. The planigram (*D*) revealed this density to be a multinodular lesion of the anterior surface of the lower lobe, directly beneath the pleura in the oblique fissure (12 cm. level).

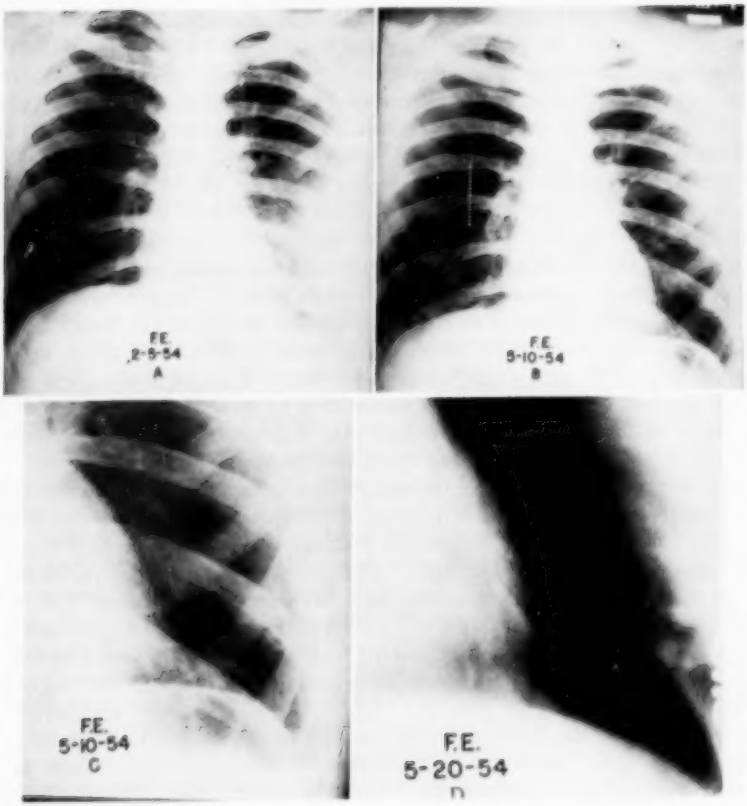


FIG. 5. Roentgenograms of a patient who had not yet been operated upon, but in whom it was possible to demonstrate by planigraphy a nodular lesion in the anterior basilar segment of the left lower lobe.

*A*. Chest roentgenogram (February 5, 1954), showing moderate left pleural effusion.

*B*. Roentgenogram (May 10, 1954), showing faint density in region of the sixth anterior rib.

*C*. Close-up view of same roentgenogram for greater detail of faint shadow which was originally interpreted as slight thickening of the pleura.

*D*. Planigram (May 20, 1954) which revealed the density shown in *B* to be a multinodular lesion of the anterior surface of the lower lobe directly beneath the pleura in the oblique fissure (12 cm. level).

The writers have observed a number of patients who have given a history of pleural pain during the course of pulmonary tuberculosis, but who never developed a pleural effusion. The pleural pain frequently disappeared as the parenchymal lesion responded to specific treatment or when it was surgically removed. Such patients are said to have "dry pleurisy." Dry pleurisy is frequently seen

with tuberculosis, and the lesions are often adherent to the chest wall. It is believed that there is a parenchymal inflammation in such cases close enough to the pleural surface to lead to local pleural irritation, pain, and be followed by pleural symphysis with fibrous adhesions. MacLean (1) has pointed out that dry pleurisy is followed by tuberculosis less often than is exudative pleurisy. This is most likely because dry pleurisy may be associated with any type of pulmonary inflammation, whereas most cases of exudative pleurisy are caused by tuberculosis.

It is generally stated that 80 to 90 per cent of otherwise unexplained cases of exudative pleurisy are of tuberculous origin (3), and this is in agreement with the clinical experience of the present writers. The high proportion of nontuberculous cases in the small series of the present study is largely a product of the manner of selection of the cases, as described above, and does not reflect the true incidence of this phenomenon.

Seven of the patients were explored because of the continued formation of fluid for months after the onset of the pleurisy. In all of these the lower portion of the lung was encased by a thin tough fibrous peel (*see* figure 3*B*). The cause for the nonspecific pleural thickening was not completely clear. The microscopic picture, however, was strikingly free of tuberculosis, and it is believed that these cases were truly nontuberculous in nature. When superficial tuberculosis does cause a pleural inflammation, the characteristic result is a localized pleural symphysis. The pleural space was preserved in all of these 7 patients, and only fibrous thickening of both pleurae was found.

The pathology of the underlying lung in these 7 cases is shown in table 3. It seems possible that the pleural inflammation was the result of a chronically active organizing pneumonia in 4 cases. Such pneumonia was found in the upper lobe in 3 instances, and in the lower lobe in one. In the latter, it was associated with cylindrical bronchiectasis. In one patient (*Case 4*) the nature of the onset of symptoms plus the surgical finding of subpleural emphysematous blebs suggested that the pleural thickening was the result of an unrecognized spontaneous pneumothorax, possibly with slight bleeding, some time in the year prior to the effusion. A peripheral focus of histoplasmosis was found in one instance. The significance of this is not clear. In one instance the underlying lung was completely normal. No case of carcinoma occurred in this series. This seems best explained by chance and the nature of the hospital population.

Whatever the cause of the fibrous pleuritis, the cause of the continued formation of fluid in these patients seems clear. In figure 3*B* surgical findings are described diagrammatically. The space left by the compressed lower lobe would ordinarily be filled by the upper lobe. But in these cases the visceral pleura was also thick over the upper lobe and prevented its filling in the dead space left by the compressed lower lobe. Apparently as a local hydrodynamic phenomenon, then, fluid was drawn into the dead space until it restored the intrathoracic pressure equilibrium. An observation was made in several cases which makes this explanation extremely likely. It was noted that the amount of fluid was remarkably constant, as observed by periodic roentgenography. After each thoracentesis,

at which 200 to 400 cc. were removed, the abnormal roentgenographic shadow was lower. Within twenty-four to forty-eight hours the fluid had reaccumulated to the pre-thoracentesis point as judged by the appearance of the roentgenograms. This was done repeatedly in 2 patients (*Cases 4* and *11*). Despite the rapid reaccumulation of fluid just after each thoracentesis, it never exceeded the original amount. From this it was deduced that the fluid was drawn into the chest only until the dead space was filled and physiologic pressure was re-established. The pleura showed no evidence of active inflammation to explain the fluid formation.

The remaining 2 cases in this group (*Cases 16* and *24*) need little comment. The pleural peels grossly resembled those seen in some of the tuberculous cases but proved to be simple fibrous tissue microscopically. In one of these (*Case 16*), the hemothorax was almost certainly the result of blunt thoracic trauma. In *Case 24* there was evidence of generalized emphysema. The hemothorax was spontaneous and was associated with a spontaneous pneumothorax. Several of the physicians who saw this patient believed from the beginning that a rupture of a bleb accounted for the illness, but others insisted that the patient be treated

TABLE 4

COMPARISON OF TUBERCULOUS AND NONTUBERCULOUS CASES

| | Tuberculous | Nontuberculous (Other Than Post-Hemorrhagic) |
|---|---|---|
| I. Clinical Findings | | |
| Systemic symptoms | Moderate, early in course | Absent; pain and dyspnea only |
| Fluid formation | Copious at first, gradually less and ceased in 6–8 weeks | Never copious but continued for months |
| Roentgenographic density | Persisted after fluid was no longer obtainable | Proportional to fluid obtainable |
| Fluid | Exudate; predominantly lymphocytes except early in course | Exudate; cell count shows polymorphonuclears, eosinophils, or lymphocytes |
| Bacteriology | Sputum, gastric, or pleural fluid may contain AFB | Negative for AFB if carefully done |
| Tuberculin | Positive | Positive or negative |
| II. Surgical Findings | | |
| Pleural space | Obliterated | Preserved |
| Pleura | Thick, fibrous, displacing lung | 1–3 mm. thick, trapping lower half of lung to small size |
| Fluid in chest | None or in small pockets | Fluid free in pleural space |
| Underlying lung | Tuberculous nodules, usually in connection with pleura and sometimes disseminated | Organizing pneumonia, emphysema, or normal |
| III. Pathologic Findings | | |
| Pleura | Granulomatous pleuritis; AFB positive | Chronic nonspecific fibrous pleuritis; AFB negative |
| Lung | Active tuberculosis, AFB positive | No evidence of TB; AFB negative |

AFB: Acid-fast bacilli.

for tuberculosis. As several competent physicians specializing in chest diseases believed that these 2 patients had tuberculosis, they have been included in this review.

The clinical differentiation of individual cases of nontuberculous effusion from those caused by tuberculosis is difficult. The clinical findings of the two groups in the present experience are contrasted in table 4, in which the differences in surgical and pathologic findings are also summarized.


## SUMMARY

The clinical, roentgenographic, surgical, and operative findings of 24 patients diagnosed as having "idiopathic pleurisy with effusion, presumably tuberculous," have been reported.

The pleura was thick, fibrous, and granulomatous in the 15 tuberculous patients. A definite parenchymal nidus was found in 12 of the 15, and multinodular tuberculosis was found in 7 patients. It appeared that the cause of the pleurisy was an actual rupture of a caseous parenchymal nodule into the pleural space. The mechanism of the effusion appeared to be the same as in the tuberculin-sensitive guinea pigs studied by Paterson in 1917.

The frequency of pulmonary tuberculosis within five years of an effusion is explained by the fact that the pleuritis is secondary to caseous tuberculosis within the lung. Surgical exploration allowed an accurate appraisal of the extent of the tuberculosis. Many of the pulmonary lesions were not even visible on retrospective study of the roentgenograms.

Seven of the nontuberculous cases were characterized by long-continued formation of free pleural fluid. The lower half of the lung was found to be trapped and compressed by a tough fibrous peel. The fluid formation appeared to be on a hydrodynamic basis. In addition, there were 2 cases of fibrothorax following intrathoracic hemorrhage.

Every patient with otherwise unexplained exudative pleurisy should be carecarefully studied (including planigraphy) for the presence and extent of tuberculosis so that appropriate therapy may be given. If the illness does not follow the typical course for primary tuberculous effusion, an exploratory thoracotomy is warranted for a more accurate diagnosis. A minimum of eight months of therapy for tuberculosis is advisable, even for the typical case of primary effusion, because of the underlying pulmonary tuberculosis.

## SUMARIO

*Hallazgos Operatorios e Histopatológicos en Veinticuatro Enfermos con Pleuresía Idiopática con Derrame, Presuntamente Tuberculoso*

Preséntanse los hallazgos clínicos, radiográficos, quirúrgicos e histopatológicos en un grupo de enfermos en quienes se diagnosticó en el Hospital Militar Fitzsimons "pleuresía idiopática con derrame, probablemente tuberculoso." En 15, se confirmó el diagnóstico de tuberculosis en la pleura y el pulmón. Nueve del grupo no revelaron signos de tuberculosis patológicamente.

Doce de los 15 casos tuberculosos revelaron un foco caseoso subpleural de tuberculosis que estaba íntimamente adherido a la película pleural granulomatosa. En 7 de estos 15

casos, se encontró tuberculosis multinodular esparcida a través del pulmón subyacente. A juzgar por esos hallazgos, parece lógica la siguiente patogenia de los derrames tuberculosos: algo tarde en la tuberculosis primaria, una lesión parenquimatosa subpleural se abre de vez en cuando en un espacio pleural libre y vacía allí su contenido caseoso. La contaminación del espacio pleural en un cutirreactor tuberculoso provoca la misma enérgica reacción pleural que Paterson describió en los cobayos tuberculinopositivos en 1917.

Queda explicada la frecuencia de la tuberculosis pulmonar en término de cinco años de un derrame por el hecho de que la pleuritis es secundaria a tuberculosis caseosa intrapulmonar. El mayor beneficio práctico derivado de la exploración quirúrgica de este grupo de enfermos fué que ésta permitió hacer una justipreciación exacta de la extensión de la tuberculosis. Muchas de las lesiones pulmonares no eran visibles ni aun en un estudio retrospectivo de la radiografía. Los enfermos que no mostraron signos de tuberculosis fueron dados de alta para volver a sus quehaceres después de una breve convalecencia de la toracotomía.

Siete de los casos no tuberculosos se caracterizaron por la formación prolongada de líquido pleural libre. Según se observó, la mitad inferior del pulmón estaba atrapada y comprimida por una recia película fibrosa. La formación de líquido parecía reconocer una base hidrodinámica. Discútese la causa de la formación de la película pleural. Además, hubo 2 casos de fibrotórax consecutivos a hemorragia intratorácica.

Todo caso de pleuresía exudativa sin otra explicación debe ser estudiado cuidadosamente (con la planigrafía inclusive) para determinar la presencia de tuberculosis, y su extensión si la hubiere, a fin de poder administrar la terapéutica apropiada. Si el caso no muestra la típica evolución del derrame tuberculoso primario, está justificada una toracotomía exploradora para hacer un diagnóstico más exacto. Conviene un mínimo de ocho meses de terapéutica para tuberculosis, aun en el típico caso de derrame primario, debido a la subyacente tuberculosis pulmonar.

RESUME

*Constatations anatomo-pathologiques et opératoires dans vingt-quatre cas de pleurésie idiopathique avec épanchement, probablement tuberculeuse*

Les auteurs rapportent les résultats des examens cliniques, radiologiques, opératoires et anatomo-pathologiques effectués au Fitzsimons Army Hospital dans un groupe de malades pour lesquels on avait fait le diagnostic de "pleurésie idiopathique avec épanchement, probablement tuberculeuse". Dans 15 de ces cas, le diagnostic fut confirmé dans la plèvre et le poumon. Aucun signe pathologique de tuberculose n'a été découvert chez 9 malades du groupe.

Parmi ces 15 cas de tuberculose, 12 présentaient un foyer sub-pleural de tuberculose caséeuse, qui était intimement fixé à l'enveloppe pleurale granulomateuse. Dans 7 de ces 15 cas, on a trouvé des lésions tuberculeuses multinodulaires disséminées dans le poumon sous-jacent. Selon ces constatations, la pathogénèse logique de l'épanchement serait la suivante: au stade avancé de la tuberculose, il arrive parfois qu'une lésion du parenchyme sub-pleural s'ouvre dans une cavité pleurale libre et y déverse son contenu caséeux. Cette contamination de la cavité pleurale chez un sujet allergique à la tuberculine y détermine une violente réaction, telle que Paterson l'a décrite en 1917 chez le cobaye allergique à la tuberculine.

La fréquence de la tuberculose pulmonaire, dans les cinq années qui suivent l'épanchement, s'explique par le fait que la pleurésie est secondaire à la tuberculose caséeuse intra-pulmonaire. Le plus grand avantage pratique dérivé de l'exploration chirurgicale de ce groupe de patients a été de permettre une évaluation exacte de l'étendue de la tuberculose. Un grand nombre de lésions pulmonaires n'étaient même pas visibles à l'examen rétrospectif des radiogrammes. Les malades indemnes de signes de tuberculose étaient rendus à leurs occupations après une courte convalescence suivant la thoracotomie.

Sept des cas non tuberculeux étaient caractérisés par la formation prolongée d'exudat pleural libre. La moitié inférieure du poumon était enfermée et comprimée par une coque

fibreuse dure. La formation de liquide paraissait d'origine hydrodynamique. La cause de la formation de cette coque fibreuse est commentée. De plus, il y avait 2 cas de fibrothorax ayant succédé à une hémorragie intrathoracique.

Tout cas de pleurésie exudative inexpliqué devra être étudié avec soin (y compris la planographie) pour rechercher la présence et l'étendue de la tuberculose, de façon à appliquer le traitement approprié. Lorsque le cas ne suit pas le cours classique de l'infection, il y a lieu de procéder à la thoracotomie exploratrice pour obtenir un diagnostic plus précis. Même lorsqu'il s'agit d'un cas type d'épanchement primaire, un traitement antituberculeux de huit mois au minimum est conseillé, en raison de la tuberculose pulmonaire sous-jacente.

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# DIFFUSE INDOLENT PULMONARY TUBERCULOSIS[1]

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## INTRODUCTION

When the lungs become the site of an active tuberculous infection, the character of the tissue reaction is dependent upon a balance between the size of the inoculum and the virulence of the offending organisms, on the one hand, and the various elements of host resistance, on the other. The pathologic changes may vary from those of an acute pneumonic process, which presumably represents intense exudation in a hypersensitive host, to the opposite extreme of an almost exclusively productive response. Theoretically, the latter process evolves when a small number of bacilli, perhaps of low virulence, superinfect a person who possesses a high degree of resistance and a low level of sensitivity.

In its early or localized form, this productive type of tuberculosis presents an appearance not unlike the fibronodular residuals of healing exudative lesions. When discovered, usually on routine examination, a roentgenographic diagnosis of arrested tuberculosis is often made. Not infrequently, however, if the modifying factors are appropriate, the process does not remain localized but gradually seeds its way throughout both lungs in a slow, insidious manner. Eventually, the process reaches an extensive, diffuse, and usually symmetrical distribution. A clinicopathologic entity results which has been comprehensively described by Ornstein, Ulmar, and Dittler under the specific heading, "chronic productive tuberculosis" (1). This form of tuberculosis is as characteristic as the caseous pneumonic or miliary phases of the disease. Nevertheless, it has been the writers' experience that, except among phthisiologists, familiarity with the manifestations of this entity is not widespread. This situation appears partially as a result of the natural confusion evolving from the application of a basic pathologic term to a clinical variant of a protean disease.

While it is apparent that the term "chronic productive tuberculosis" is quite accurate from a strictly pathologic standpoint, unfortunately some uncertainty concerning its exact implications exists. Through common usage, it is frequently (and in a pathologic sense, correctly) applied to other clinical types of tuberculosis in which productive elements of a reparative nature exist and sometimes even predominate. Consequently, the term seems to have lost its original clinical connotation and is rarely used to distinguish the clinicopathologic entity to which it originally applied. Quite obviously, then, if it cannot be reserved for those cases conforming to the original description, a new designation must be devised which is both descriptive and discriminating. Therefore the present writers propose the term *diffuse indolent pulmonary tuberculosis* to designate the clinical form of tu-

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berculosis in question. Regardless of its designation, however, it is believed that a decreasing awareness of the concept requires that it be re-emphasized and redefined.

## PATHOLOGY

Diffuse indolent, or chronic productive, pulmonary tuberculosis is characterized by a tissue response which is almost exclusively productive. The productive reaction consists of the formation of a specific type of granulation tissue which is primarily composed of the epithelioid tubercle so familiar as the basic tissue change in tuberculous lesions. The tubercle, which is not unlike a small benign tumor, is made up of a solid focus of epithelioid cells, Langhans' giant cells, a peripheral border of lymphocytes, a few polymorphonuclear leukocytes, and the later development of a surrounding zone of fibrous tissue.

There is still some disagreement in regard to the very beginning of the productive process, and many investigators believe that an initial exudative phase always occurs (2). This may be brief and extremely slight, however, and, in the absence of significant hypersensitivity, is soon overshadowed by the productive reaction. It is the existence of the above type of lesion without significant exudative components which accounts for the prolonged and relatively symptomless course and the difficulty in establishing a bacteriologic diagnosis.

Although individual tubercles may coalesce and undergo central caseation, the latter process is seldom extensive and cavity formation is not common. More often, the tubercle undergoes fibrosis with conversion into a hard, fibrotic nodule, which may closely simulate a silicotic lesion. When healing of the individual productive tubercles takes place, there is scarring and shrinkage with associated dilatation of the surrounding alveoli. If the disease has gained very extensive distribution, the perifocal emphysema thus produced may lead to significant disability.

Extension of the process proceeds slowly over a period of many years and occurs as the result of temporary episodes of caseation with contiguous seeding into the surrounding tissues or through connecting bronchioles. Occasional brief and mild episodes of exudation take place and account for the clinical flareups which occur in the course of the illness. On rarer occasions, the exudative phase suddenly becomes dominant and the disease process then converts to a caseous pneumonic form of tuberculosis.

As with other types of tuberculosis, the initial infiltrate is most likely to occur in the upper portions of a lung, usually in the apex. Except for intermittent periods of stability, the infection then gradually but relentlessly spreads toward the base. During the course of the disease the opposite lung becomes involved. Again, the apex is likely to be first affected, and the process creeps slowly caudad in a halting manner, so that late in the course there is likely to be a diffuse bilateral distribution of the fine nodular lesions. The presence of the chronic insult for a period of years eventually results in fibrosis and emphysema, with resultant pulmonary hypertension and perhaps failure of the right side of the heart.

## CLINICAL MANIFESTATIONS

In its classical form, the clinical picture of diffuse indolent pulmonary tuberculosis is far different from that which is usually associated with other types of advanced pulmonary tuberculosis. Symptoms are characteristically minimal or completely lacking, even late in the course of the disease. Probably because a long period is required for sufficient complaints to evolve and provoke the patient to seek medical advice, the disease is seen predominantly after the fourth decade of life. The discovery of the process at this time is often the result of a fortuitous roentgenographic examination performed during some routine evaluation. Careful inquiry may elicit a history of mild cough of long duration, but usually very little more. Physical examination is likewise not particularly helpful. A few fine apical rales may be detected, and evidence of pulmonary emphysema may be present, but more frequently physical findings are inconclusive or entirely absent. The tuberculin reaction is but weakly positive, denoting a low degree of sensitivity. Sputum is characteristically scanty and only occasionally does it contain tubercle bacilli. This dearth of organisms may render twenty or more negative sputum examinations before a positive specimen is encountered. In particularly difficult instances, a bacteriologic diagnosis can usually be established by cultural methods or guinea pig inoculation of concentrated sputum specimens and gastric washings. Even these procedures, however, may require many repetitions before a positive result is obtained.

The indolent course is sometimes punctuated by mild clinical flareups manifested by low-grade constitutional and respiratory symptoms and a greater ease of demonstration of tubercle bacilli. Following these episodes, which are characteristically of short duration, bacilli once again become scanty and there remain few or no outward evidences of disease despite progressive pulmonary dissemination.

Over a period of years, perhaps twenty or more, complicating bronchitis and emphysema may become manifest and cause an irritating cough or exertional dyspnea. Cyanosis and fatigability may reflect an underlying hypoxia. Death from this type of tuberculosis is usually due to sudden conversion to an exudative form, occurring either singly or in combination with cor pulmonale, or respiratory insufficiency resulting from emphysema and fibrosis. Even though the chances for a relatively long life span are good, either with or without therapy, the ultimate prognosis is poor since the disease in most cases is gradually progressive. Hemoptysis, in single or repeated bouts, has been noted with some frequency by others (3), but has been unusual in the writers' experience, as has the development of extrapulmonary foci.

## ROENTGENOGRAPHIC FINDINGS

Roentgenographically, diffuse indolent pulmonary tuberculosis may vary in extent from an initial small upper lobe infiltrate to the advanced picture of diffuse bilateral, more or less symmetrical shadows, the latter being the most commonly recognized. The individual nodules are sharp and somewhat granular

in appearance due to the presence of surrounding perifocal emphysema. These small nodular and linear densities are usually more concentrated in the upper and medial zones of the lungs, sometimes giving a hilar-infiltrating, fanlike configuration. The over-all appearance of the disease process might be appropriately described as "fine feathery" shadows or "salt and pepper" lungs. Lymph nodes do not appear enlarged, and confluency and cavitation are not common. Generalized emphysema is apparent in long-standing cases.

## DIFFERENTIAL DIAGNOSIS

Although the diffuse indolent form of pulmonary tuberculosis is not common, it is far from rare. It has been the writers' experience that the clinical similarity of the indolent form to other disorders which produce diffuse pulmonary involvement often requires consideration of this type of tuberculosis in differential diagnosis. From the foregoing statements, it is apparent that such factors as an absence or minimum of symptoms, difficulty in demonstrating tubercle bacilli in the sputum, and unfamiliarity with the roentgenographic picture of this type of tuberculosis contribute to the diagnostic problem.

It is interesting that many of the writers' cases were given a presumptive diagnosis of Boeck's sarcoid, either initially or after an intensive search for tubercle bacilli had proved fruitless. A number of other diseases which can produce similar pictures were likewise considered in some instances, e.g., pneumoconiosis, silicotuberculosis, histoplasmosis, lymphangitic carcinoma, atypical pneumonia, and diffuse interstitial idiopathic fibrosis. Diagnostic studies along these lines often received corresponding priority, and it was only after other conditions had been satisfactorily excluded that tuberculosis became the outstanding probability. In fact, it was the frequent, surprising appearance of this type of tuberculosis in situations of this sort which provoked the present writers' interest in this problem. It was noted, also, that in many of the cases the tuberculous process, when found to be present, was usually deemed atypical; however, it should be emphasized that it is "typical of its type."

## THERAPY

For many years the therapy of diffuse indolent pulmonary tuberculosis has presented an unusually difficult problem. During the pre-streptomycin era it was repeatedly emphasized that bed rest, sanatorium care, and collapse measures had little effect on the course of the disease. It was generally recommended that the patient be allowed to lead his usual life, entering the sanatorium only when periodic exacerbations occurred (3). Ulmar (4) stated that it was almost criminal to confine the victim of this form of tuberculosis in a sanatorium, where little could be done to alter the gradual progression of the pulmonary lesions. Such a patient was generally considered to be rather fortunate in that he had a relatively benign form of the disease and could look forward to a very long and asymptomatic course. However, the eventual prognosis was dire indeed, and the patient usually succumbed to an acute caseous pneumonic flareup or died as a victim of emphysema, fibrosis, anoxemia, and cardiac failure.

The introduction of specific chemotherapeutic agents has necessitated a definite revision of the above concept of management and prognosis. Although the response of diffuse indolent tuberculosis to antimicrobial agents is anything but dramatic, it has been the writers' experience that some improvement can be expected in almost every case in which streptomycin-PAS is employed. It has been the present writers' practice to combine chemotherapy with relatively short periods of bed rest, and pneumoperitoneum has frequently been utilized as an adjunctive measure, even though the value of this form of collapse has not been separately established.

It is to be emphasized that the above therapy will only occasionally result in marked regression of the pulmonary lesions; however, some degree of improvement or at least an arrest of the progression of the disease can nearly always be expected. While the latter response falls far short of an ideal result, it at least affords promise of avoiding the crippling effects of late emphysema and fibrosis and greatly improves the over-all prognosis. None of the writers' patients received streptomycin-PAS for periods longer than five and one-half months. It seems probable that longer courses of chemotherapy and the use of isoniazid might further brighten the outlook.

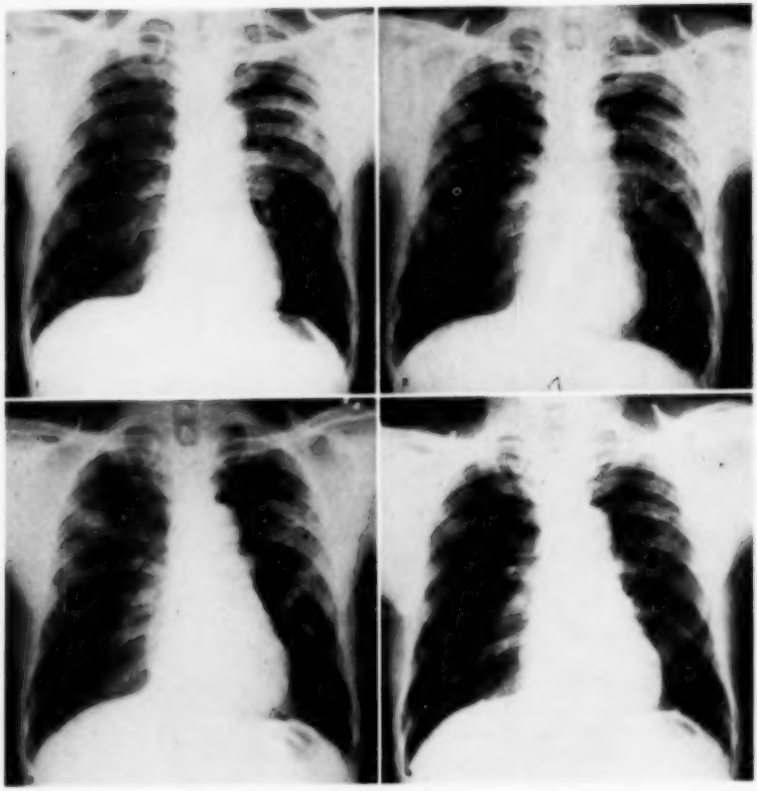
## CASE REPORTS

*Case 1.* L. P., a 52-year-old white male laborer, was hospitalized at the New Orleans Veterans Administration Hospital in 1948 because of a genitourinary tract infection. A routine roentgenographic examination of the chest at that time disclosed evidence of pulmonary disease (figure 1). The lesion in question appeared as a fine, nodular infiltration, occupying the area between the upper borders of the second and fourth left anterior ribs, and seemed to emanate from the left upper hilar area. No signs or symptoms of respiratory disease were elicited. Comparison of this film with a previous roentgenogram of April 23, 1947, disclosed, in retrospect, that the lesion had been present at that time in a much less extensive and barely detectable form.

Following the discovery of the pulmonary pathology, the patient was subjected to extensive diagnostic studies in an effort to clarify the etiology, both during the initial hospitalization and in the course of many subsequent periods of observation. He remained consistently asymptomatic from a respiratory standpoint, and repeated physical examinations disclosed no abnormalities of the lungs. Despite this asymptomatic state, however, there occurred progressive dissemination of the fine, nodular process throughout the middle two-thirds of the left lung. By August 9, 1950, the infiltration had spread to the midportion of the right lung field (figure 2). By September 12, 1951, a multitude of sputum concentrates for acid-fast bacilli, many sputum cultures for fungi, cultures of sputum and gastric washings for tubercle bacilli, skin tests with blastomycin and coccidioidin, bronchoscopy, liver function studies, and roentgenograms of the hands and feet had been performed and found to be either negative or normal. The tuberculin skin test had varied from negative to weakly positive in first strength. When the test with first-strength tuberculin was negative, testing with second-strength antigen was consistently positive.

Throughout the years of study, varied and multiple etiologies had been considered. These included Boeck's sarcoid, atypical pneumonia, bronchogenic carcinoma, mycotic infection, lipoid pneumonia, and tuberculosis. Because of other evidences of syphilis and strongyloidiasis, involvement of the lungs by these diseases was even given some consideration.

The last period of prolonged hospitalization was begun on November 3, 1951, because of progressive increase in the extent of the pulmonary shadows. Again, there were no con-



*Case 1* (L. P.)

FIG. 1. November 18, 1948. Erect postero-anterior film of chest showing presence of a fine nodular infiltration occupying the area between the second and fourth left anterior ribs. Patient had no respiratory symptoms, and sputum studies were negative for tubercle bacilli.

FIG. 2. August 9, 1950. Note very slight extension of the infiltration in the left lung and early spread to the right mid-lung field. Sputum still negative for tubercle bacilli and patient asymptomatic.

FIG. 3. January 2, 1952. Lesions occupy middle two-thirds of both lung fields, the most marked degree of extension observed. Sputum remained negative, but a culture of gastric contents was positive for tubercle bacilli at this time. Surgical biopsy of lung performed twelve days later and diagnosis of tuberculosis established.

FIG. 4. January 9, 1953. Patient received course of streptomycin-PAS between this and previous film. Marked regression of the bilateral lesions has occurred, especially on the right.

stitutional symptoms or signs referable to the chest. On this occasion, a culture of gastric contents was finally positive for tubercle bacilli but also produced an acid-fast organism thought to be *Nocardia asteroides*. Sputum concentrates and a sputum culture for fungi were negative. A film taken on January 2, 1952, showed the pulmonary lesions to occupy the

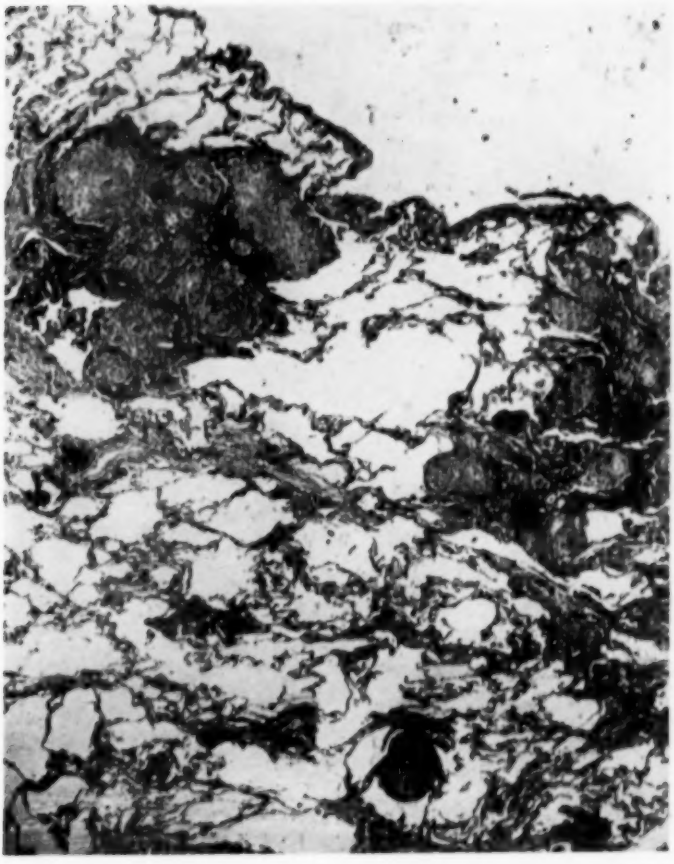


FIG. 5. *Case 1* (L. P.). Low-power magnification (× 42) of lung biopsy specimen showing small discrete nodules with associated perifocal emphysema. The nodules are composed of conglomerate tubercles and grossly measure 1 to 2 mm. in diameter. Note absence of exudative components. These changes are typical of the exclusively productive reaction which characterizes diffuse indolent tuberculosis.

middle two-thirds of both lung fields, the most marked degree of extension which had been noted (figure 3).

Because of the confusion regarding the diagnosis, the steady progression of the disease, and the isolation of two possible etiologic agents, a surgical biopsy of the left upper lobe was performed on January 14, 1952. The pleural surface of the surgical specimen showed some evidence of fibrous thickening. Examination of the cut surface disclosed the parenchyma to be studded with tiny gray-white nodules which involved practically the entire specimen. Most of these nodules were discrete and nonconfluent, each measuring an average of 1 to 2 mm. in diameter. Microscopic findings were compatible with tuberculosis of a productive form (figures 5 and 6). Cultures of the specimen were positive for both *Mycobacterium tuberculosis* and an acid-fast fungus finally identified as *Micromonospora* (not

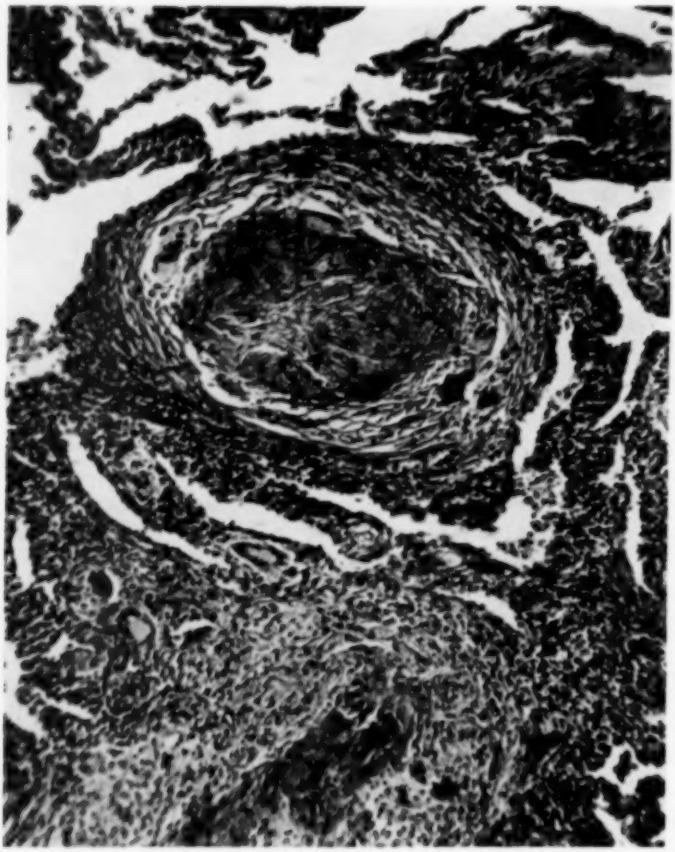


FIG. 6. *Case 1* (L. P.). High-power view (× 90) of lung biopsy specimen showing a typical noncaseous tubercle with central hyalinization. Conglomerate tubercles of this type form the tiny nodules which account for the roentgenographic appearance of diffuse indolent tuberculosis.

considered pathogenic). The acid-fast organism previously obtained by gastric culture was subsequently identified as a saprophytic acid-fast bacillus.

On the day of surgery, a course of streptomycin-PAS was begun. Pneumoperitoneum was induced on March 5, 1952, but discontinued on April 4, 1952, because of the presence of an inguinal hernia. Streptomycin-PAS therapy was discontinued on June 26, 1952, after 120 gm. of streptomycin had been administered. On February 29, 1952, a sputum concentrate revealed the presence of rare acid-fast bacilli. Ten subsequent concentrates were negative.

On a program which included the above-described antimicrobial therapy and bed rest, there was marked resolution of the bilateral pulmonary lesions and the patient gained 27 pounds in weight. The latter was felt to be due in part to a better diet which was available to the patient in the hospital. He was discharged on July 1, 1952, with instructions to follow

a program of modified bed rest at home. At the time of the last follow-up examination on March 9, 1953, he was doing well and the pulmonary shadows had shown some slight further regression (figure 4).

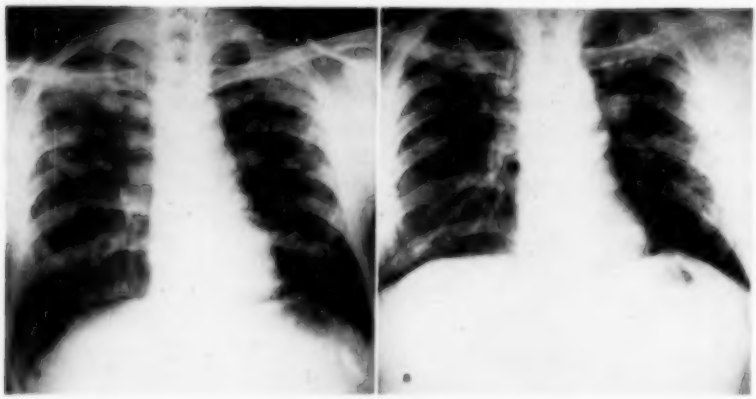
A number of pertinent points are illustrated by this case. Notably, the difficulty of the diagnostic problem is brought out by the fact that most of the common—and even some bizarre—lung ailments were seriously considered during the course of the patient's disease. Moreover, the characteristic sparsity of acid-fast bacilli in this form of tuberculosis further contributed to the difficulties involved. The slow extension of the pulmonary lesions over a period of years from an original small upper lung focus to extensive bilateral disease, without notable impairment of the general health, is exemplified. The clearing that was achieved by the use of antimicrobial agents was gratifying. Complete clearing of a process which produces a large amount of scarring is not to be expected; however, it is hoped that the active pathologic elements were suppressed to a degree sufficient to retard reactivation of the disease and resulting late complications.

*Case 2.* G. C., a 39-year-old Negro male laborer, was first seen at the Veterans Administration Hospital, New Orleans, Louisiana, on September 3, 1952, for further evaluation of pulmonary disease which had been detected on a pre-employment roentgenographic examination of the chest nine weeks before entry. Some thirty years before, the patient's father died of pulmonary tuberculosis, and since that time the patient had had frequent "colds" manifested chiefly by a mildly productive cough. However, it is noteworthy that he never considered himself ill through the years and was able to carry out heavy labor with little difficulty. During the six-month period before entry, the patient had noted a gradual weight loss, which he attributed to irregular eating habits, since he felt well and his appetite had remained unimpaired. Approximately seventeen days before admission he developed one of his usual colds, with cough, mild dyspnea, and a sensation of feverishness. All of these symptoms subsided spontaneously, however, a few days before he was admitted to the hospital. He could not recall a previous history of hemoptysis, night sweats, chest pain, or exposure to silicates.

Physical examination disclosed an afebrile person who gave the general appearance of being well. There were scattered fine rales throughout both lung fields and evidence of mild emphysema, but no other pertinent physical abnormalities.

Admission roentgenogram of the chest (figure 7) revealed the presence of fine nodular and linear shadows scattered throughout the major portion of both lung fields and seeming to radiate from the hilar zones. Some of the shadows exhibited a tendency toward confluency in the upper lung areas, but no definite cavitation or adenopathy could be detected. It is interesting that at this point a number of diagnoses were suggested by various observers, chief among which were Boeck's sarcoid, pneumoconiosis, mycotic infection of the lungs, chronic interstitial pneumonitis, silicotuberculosis, and uncomplicated tuberculosis. The last-mentioned possibility was either completely omitted or lightly considered by most of the physicians with whom the case was discussed. By far, sarcoidosis received the greatest emphasis.

The tuberculin skin test was 2-plus with first-strength purified protein derivative, and concentrated sputum specimens consistently revealed large numbers of acid-fast bacilli. The patient was placed on a program of bed rest and, on October 24, 1952, daily streptomycin-PAS therapy was begun. At present, the patient has felt well consistently and has remained afebrile. Tubercle bacilli disappeared from the sputum shortly after the institution of antimicrobial therapy, and serial roentgenographic examinations of the chest have disclosed only minimal regression of the pulmonary lesions (figure 8) during a seven-month period of hospitalization.



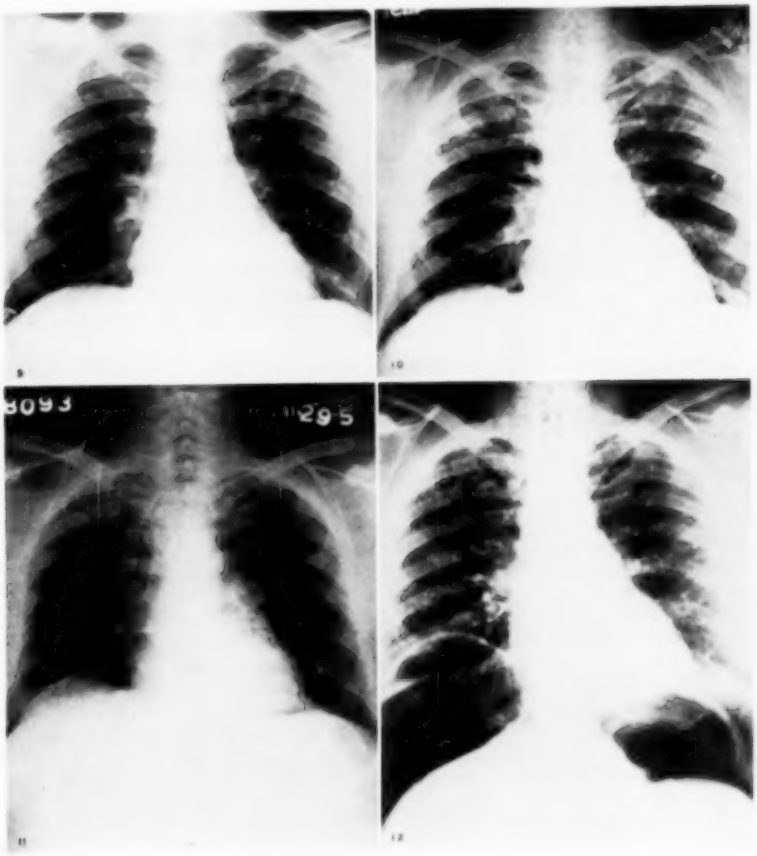
*Case 2* (G. C.)

FIG. 7. September, 1952. Erect postero-anterior film of chest showing presence of linear and small nodular shadows scattered throughout the greater part of both lungs; there is a slight tendency toward confluency in the upper portions of the lung fields. Patient was asymptomatic, but acid-fast bacilli could easily be found in the sputum.

FIG. 8. April 14, 1953. Slight clearing of the confluent pulmonary shadows has occurred after a seven-month period of bed rest and five months of therapy with streptomycin-PAS; however, the total extent of the nodular lesion remains essentially unchanged. Sputum became negative for tubercle bacilli after institution of drug therapy.

The course of events in this patient demonstrates that the syndrome under consideration can be present in advanced stages without serious impairment of the general health. Indeed, the patient had no suspicion of the existence of significant pulmonary disease prior to its discovery on a routine roentgenographic examination. At that time he did not feel or appear to be ill, and was performing heavy labor in spite of the fact that the disease process involved practically every visible portion of lung tissue. The periodic colds during the course of the illness and just prior to the time of admission may well have represented caseous flare-ups, which were suppressed after a short duration by constitutional factors. The ease of demonstration of the organisms in the presence of caseous elements in this patient is in sharp contrast to the difficulty encountered in the previous case, in which the pathologic process was almost exclusively productive during all observations. The multiplicity of diagnostic possibilities mentioned again emphasizes the confusing clinical picture.

*Case 3.* H. R., a 51-year-old white male laboratory technician, was admitted to the Veterans Administration Hospital, New Orleans, Louisiana, for the first time on April 29, 1948, for further evaluation of "highly suspicious" shadows discovered on a routine roentgenogram of the chest. For ten years he had had a chronic, early morning cough, with production of very small amounts of white sputum. He had experienced mild exertional dyspnea for several years, but had been overweight during this time. He did not consider himself ill at the time that the pulmonary lesions were detected, and could not recall having had fever,




*Case 5* (H. R.)

FIG. 9. November 28, 1944. Earliest available chest roentgenogram showing linear and nodular lesions in the upper portions of both lungs.

FIG. 10. April 29, 1948. Film taken at time of first hospital admission, shortly after discovery of "highly suspicious" shadows on routine employment film. Note bilateral increase in extent of pulmonary lesions over a period of four years. Patient described minimal cough but no other symptoms. Sputum and gastric washings consistently negative for tubercle bacilli.

FIG. 11. November 29, 1950. No specific therapeutic measures were employed between this and previous film; further progression of disease has occurred. Patient still described only a mild cough and had gained 15 pounds in weight. Acid-fast bacilli could only occasionally be found in the sputum.

FIG. 12. April 3, 1953. After drug therapy, moderate clearing of pulmonary lesions has occurred, but many scattered nodular shadows are still visible. Patient remains clinically well. Sputum negative for tubercle bacilli.

hemoptysis, night sweats, or chest pain. His mother had been treated with bed rest for one year for pulmonary tuberculosis, and an aunt and uncle had died from the same disease.

Other than the presence of moderate obesity, the admission physical examination was unrevealing.

A roentgenogram of the chest (figure 10) disclosed the presence of diffuse, fine, nodular and linear densities occupying the upper one-third of each lung field. These lesions were slightly more prominent on the right. Comparison of this film with previous annual employment roentgenograms revealed that the pulmonary disease had been present since the earliest available film of November 28, 1944 (figure 9) and had gradually increased in extent from the original small, bilateral, subapical foci.

A skin test was negative with first-strength tuberculin but 2-plus with second-strength purified protein derivative. Thirteen concentrated sputum specimens, three gastric cultures, and a sputum culture were negative for tubercle bacilli. Skin tests with histoplasmin and coccidioidin were also negative.

Treatment during hospitalization consisted of bed rest only, and the patient remained afebrile and asymptomatic. No significant change was detected on serial roentgenographic studies, and he was discharged on April 2, 1949. Within two months after leaving the hospital, he returned to full activity as a laboratory technician. Follow-up studies indicated gradual progression of the lung pathology (figure 11), however, and he was therefore readmitted on October 19, 1950. He had gained 15 pounds in weight during the interim.

A history of mild cough and minimal exertional dyspnea was again obtained, but there were no other significant symptoms or abnormal findings. Of 15 sputum concentrates, 4 were positive for acid-fast bacilli (rare on all occasions).

A program of complete bed rest was instituted, and on December 7, 1950, daily streptomycin-PAS therapy was begun. The dosage of the former drug was varied and was alternated with dihydrostreptomycin because of disturbing vestibular symptoms. At completion of a total of 67 gm. of these two drugs, chemotherapy was discontinued on April 6, 1951. Pneumoperitoneum, which had been induced on January 20, 1951, was maintained. On April 13, 1951, the patient was discharged from the hospital with instructions to observe modified bed rest at home. Since that time, sputum examinations have remained consistently negative for acid-fast bacilli, and follow-up roentgenograms through April 3, 1953 (figure 12) have revealed moderate clearing of the pulmonary lesions. The patient now follows a program of slightly restricted activity but has not returned to work. He remains clinically well.

It was possible to follow the course of indolent lesions over a period of eight years in the lungs of this patient. During this period his health remained unimpaired in spite of extensive spread of the disease; without therapeutic intervention, he would probably have progressed to the full-blown diffuse picture. This may eventually occur despite the treatment he received, but such a distressing outcome was certainly delayed and may have been prevented.

*Case 4.* H. S., a 53-year-old Negro truck driver, was admitted to the Veterans Administration Hospital, New Orleans, Louisiana, for the first time on July 26, 1948, complaining of hoarseness of thirty years' duration and pain on swallowing and generalized weakness of three weeks' duration. History revealed that the patient underwent surgery for a tonsillar abscess in 1918. Since then, he had experienced recurrent difficulty in talking, characterized by ability to speak only in a whisper. This condition became progressively worse, and in 1940 he finally sought admission to a hospital. Although he did not know what diagnosis was established at that time, and hospital records were unavailable, a roentgenogram of the chest dated August 5, 1940 (figure 13) disclosed a small area of infiltration in the left pulmonary apex, and it is probable that he had been considered to have pulmonary

tuberculosis. During the following six years he was hospitalized on several occasions, and records of hospitalizations during 1945 and 1946 indicate that he was regarded as having "pulmonary tuberculosis, bilateral, moderately advanced, inactive," and "hoarseness due to scarring of the left vocal cord." Sputum and gastric examinations were consistently negative for tubercle bacilli during the above periods of observation. In spite of repeated hospitalizations, the patient's hoarseness was never greatly benefited by therapy, and during the early part of 1948 he experienced a marked aggravation of this symptom.

On admission, additional complaints included headaches, pain around the eyes, dyspnea and precordial pain on exertion, and a mild, slightly productive cough of many years' duration. However, the patient had gained 5 to 10 pounds in weight during the past year and denied fever, sweats, or hemoptysis.

Physical examination disclosed a well-developed, well-nourished, elderly Negro male who spoke in a hoarse whisper. His temperature was 98° F., pulse 76, blood pressure 130 systolic and 80 diastolic in mm. of mercury, and weight 142 pounds. Examination of the heart and lungs was not remarkable, nor was the remainder of the physical examination. Indirect and direct laryngoscopy revealed numerous white, papular lesions in the interarytenoid area together with injection and granulation tissue along the left vocal cord.

Admission roentgenogram of the chest (figure 14) was reported by the hospital radiologist as showing a diffuse, varying-sized nodularity throughout the upper halves of both pulmonary fields, which had an almost metallic look, suggesting that a large part of the roentgenographic changes might be due to residual Lipiodol® from previous bronchographic examination. The lower half of each pulmonary field appeared somewhat emphysematous. It was the radiologist's impression that, if Lipiodol® was not present in the patient's tracheobronchial tree, then conditions which must be considered were (*1*) moderately advanced pulmonary tuberculosis, (*2*) Boeck's sarcoid, (*3*) pneumoconiosis with confluency and possible superimposed tuberculosis, and (*4*) fungus disease.

Tuberculin skin test was 3-plus in the first strength. Laryngeal biopsy disclosed the presence of noncaseating tubercles. Fourteen sputum and gastric examinations were negative for tubercle bacilli.

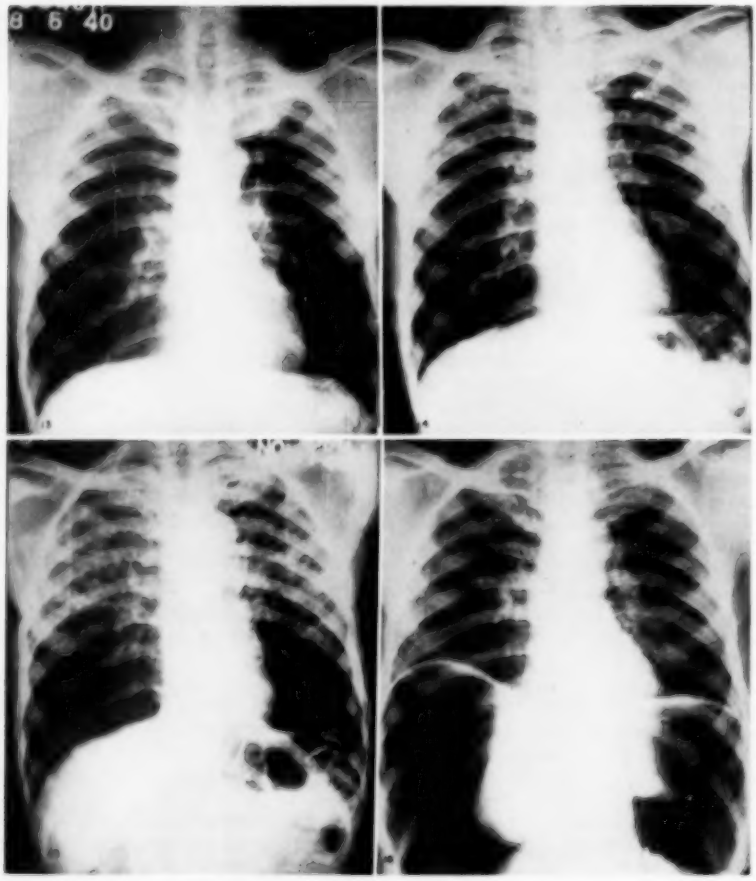
The patient received no specific therapy. On bed rest alone, he soon became generally asymptomatic, although his hoarseness remained the same. Subsequent roentgenograms of the chest disclosed no significant change in the extent or character of the pulmonary lesions, and the patient was discharged from the hospital on October 28, 1948, to a program of restricted activity at home. His diagnoses at that time were moderately advanced arrested pulmonary tuberculosis and tuberculosis of the larynx.

Following the patient's release from the hospital he did quite well until the fall of 1949, when he experienced the rather sudden onset of a severe productive cough, marked fatigue, weight loss, fever, increasing hoarseness, and dysphagia. Because of progression of these complaints, he was readmitted to the hospital on October 31, 1949.

Physical examination at this time disclosed the patient to be weak, emaciated, and obviously ill. His voice had a hollow, whispered quality. His temperature was 101.4° F., pulse 120, blood pressure 110 systolic and 80 diastolic in mm. of mercury, and weight 108 pounds. Many fine and coarse rales were scattered throughout both lung fields. Laryngoscopy disclosed the epiglottis to be markedly ulcerated, with a large defect in its superior portion. The remaining laryngeal structures were edematous and injected.

Roentgenogram of the chest on admission (figure 15) revealed an extensive, soft, flocculent infiltration involving the upper two-thirds of both lung fields. Within the areas of infiltration there were many zones of increased lucency which suggested the presence of multiple small, poorly-defined cavities. Intermittent sputum examinations were positive for acid-fast bacilli, but the majority were negative. Tuberculin skin test was one-plus in the first strength. Microscopic examination of a biopsy specimen from the epiglottis revealed the presence of a chronic inflammatory reaction with a few areas suggestive of granulomatous tissue.

Treatment consisted of complete bed rest, 91 gm. of dihydrostreptomycin, and induction




*Case 4* (H. S.)

FIG. 13. August 5, 1940. Earliest chest film available showing small area of infiltration in apex of left lung. Hoarseness represented patient's only complaint.

FIG. 14. July 26, 1948. Showing progression of disease process over a period of eight years. The upper halves of both lungs are involved by a diffuse, varying-sized nodularity. Patient had developed mild cough, slight exertional dyspnea, and an increase in hoarseness. Sputum and gastric washings were consistently negative for tubercle bacilli, but laryngeal biopsy revealed noncaseating tubercles.

FIG. 15. November 1, 1949. Film taken at time of patient's readmission to the hospital, showing marked increase in the extent of the pulmonary lesions which involve the upper two-thirds of both lung fields. Associated clinical symptoms consisted of rapid onset of productive cough, weight loss, and fever. Acid-fast bacilli could only occasionally be demonstrated in the sputum.

FIG. 16. April 11, 1953. Most recent follow-up film, which reveals only a few residual linear densities in the upper lung fields. This situation has remained unchanged for a full two years.

of pneumoperitoneum on March 21, 1950. On this therapy, gratifying clinical improvement took place; fever gradually subsided, symptoms abated, and hoarseness decreased. A weight gain of 39 pounds was recorded. Sputum generally remained negative for tubercle bacilli and serial roentgenograms of the chest revealed marked resolution of the bilateral pulmonary lesions. The patient was discharged from the hospital on August 2, 1950, to a program of restricted physical activity at home and maintenance of pneumoperitoneum on an outpatient basis.

At the time of the most recent follow-up examination on April 11, 1953, a roentgenogram of the chest (figure 16) disclosed only a few residual nodules and strands in the upper lung fields. The patient was doing well from a clinical standpoint and complained only of moderate hoarseness. Sputum had remained consistently negative for tubercle bacilli, and he continued to observe slightly restricted activity. Pneumoperitoneum had been maintained.

Although the patient undoubtedly had both pulmonary and laryngeal tuberculosis for some years prior to its detection in 1940, his case nevertheless afforded an excellent opportunity to observe the course of the disease during the ensuing thirteen years. The indolent character of this form of tuberculosis is again illustrated by the patient's lack of systemic and respiratory symptoms, despite a gradual progression of the pulmonary lesions from a small apical focus to diffuse symmetrical involvement of the upper halves of both lungs over an eight-year period. During this time, bacteriologic studies were consistently negative and the pulmonary disease was repeatedly regarded as arrested or inactive.

The sudden conversion of the indolent process to an acute, rapidly progressive form, after many years, emphasizes one of the hazards to be encountered and sharply indicts the tendency to regard this type of tuberculosis as benign.

The initial impressions of the radiologist are of interest in that they serve to point out the roentgenographic characteristics of diffuse indolent pulmonary tuberculosis and the differential diagnostic problems involved.

From a pathologic standpoint, it might be assumed that the noncaseating tubercles demonstrated by laryngeal biopsy were representative of a similar histologic reaction to be found in the lungs.

Therapeutically, it would seem that the administration of specific antimicrobial agents during the patient's initial hospitalization might have prevented the later flareup of the disease process and, in retrospect, appears to have been clearly indicated. Certainly, the patient's subsequent response to streptomycin and pneumoperitoneum was highly gratifying.

## SUMMARY

An effort has been made to describe a diffuse indolent form of pulmonary tuberculosis, designated in the past as "chronic productive tuberculosis." Either because of confusion related to the exact implications of this term or because of a present-day tendency to apply it loosely as a designation of fibrotic residuals of inactive tuberculosis, a somewhat limited awareness of this specific clinicopathologic entity appears to exist. In any even, the present writers have found the phrase *diffuse indolent pulmonary tuberculosis* a useful substitute for the older term. It seems both appealing and appropriate—diffuse to indicate the tendency toward widespread pulmonary involvement, and indolent to describe

the lazy manner in which the disease process gradually browses downward through the lungs over the course of many, essentially symptomless, years.


## SUMARIO

*Tuberculosis Pulmonar Indolente Difusa*

Trátase aquí de describir una forma indolente y difusa de tuberculosis pulmonar, denominada en el pasado "tuberculosis productiva crónica." Ya debido a la confusión relacionada con las inferencias exactas de ese término o debido a la tendencia actual a aplicarlo imprecisamente como designación de los residuos fibrosos de una tuberculosis inactiva, o quizás debido a falta general de interés en la tisiología, parece existir un reconocimiento algo limitado de esa específica entidad clínicopatológica. De cualquier modo, a los AA. la frase "tuberculosis pulmonar indolente difusa" les ha resultado un substituto útil del término más antiguo. Les parece llamativo y apropiado: difusa para indicar la tendencia a una invasión pulmonar generalizada e indolente para describir la forma perezosa en que el proceso patológico se desliza paulatinamente hacia abajo a través de los pulmones en el transcurso de muchos años, en conjunto asintomáticos.

## RESUME

*Tuberculose pulmonaire diffuse "indolente"*

Les auteurs tentent de décrire une forme torpide de tuberculose pulmonaire dénommée antérieurement "tuberculose chronique fibreuse". Que ce soit par une confusion relative à l'implication exacte du terme, ou en raison de la tendance actuelle à l'appliquer de façon imprécise pour désigner les lésions fibreuses, séquelles d'une tuberculose stabilisée, ou encore par un désintéressement général à l'égard de la phtisiologie, il semble exister une connaissance relativement limitée de cette affection particulière. En tout cas, les auteurs estiment que l'expression "tuberculose pulmonaire diffuse indolente" peut être avantageusement substituée à la désignation ancienne. Elle semble à la fois suggestive et appropriée—diffuse, pour indiquer la tendance à l'envahissement du poumon—indolente, pour décrire la progression paresseuse du processus pathologique descendant dans le poumon au cours d'années nombreuses et essentiellement asymptomatiques.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# THE AFTER-HISTORY OF PULMONARY TUBERCULOSIS[1]

## V. Moderately Advanced Tuberculosis

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### INTRODUCTION

Despite the considerable interest in moderately advanced pulmonary tuberculosis, there are only a few papers in the medical literature dealing with this stage of disease, the treatment of which so frequently requires the exercise of nice clinical judgment. The morbidity and mortality associated with moderately advanced tuberculosis would be expected to occupy a position between the extremes observed in minimal and in far advanced disease. It is worth while to consider whether this position is nearer the one extreme or the other.

The present study was undertaken to examine the clinical course of a group of persons with moderately advanced tuberculosis. As in two previous investigations (1, 2), the clinical status of each person was assessed at the time of diagnosis and at succeeding annual intervals and the data were combined to form a composite after-history. Since chemotherapy was given in only a few instances, the after-history is an indication of the results achieved without the use of these agents.

### ORGANIZATION OF INVESTIGATION

#### *Material*

In a review of all reported diagnoses of pulmonary tuberculosis made during the years 1938–1948 among residents of eight semi-rural counties, 312 cases of moderately advanced disease were found. This represents substantially the entire incidence of moderately advanced tuberculosis in a geographical population during an eleven-year period. Of the 312 cases, 73 were originally reported as minimal tuberculosis, 217 as moderately advanced tuberculosis, and 22 as far advanced tuberculosis. In no instance had a diagnosis of tuberculosis previously been made. While the clinical material consists largely of patients observed by the staff of the Hermann M. Biggs Memorial Hospital, there are a number of district residents included who were admitted either to voluntary hospitals or to facilities of the Veterans Administration.

Forty-three persons, on whom only meager clinical data were obtainable, were excluded from the study. Of these, 35 were lost to observation within six months of diagnosis, while in the remainder evidence to support the diagnosis of pulmonary tuberculosis was not available. Of the 43 persons excluded, 6 were known to have active tuberculosis at the time of diagnosis, while 17 had arrested tuberculosis, the status of disease being unknown in 20.

Thus, the clinical material presented here consists of 269 persons who were

[1] From the Hermann M. Biggs Memorial Hospital, Ithaca, New York.

first discovered to have moderately advanced tuberculosis during the years 1938–1948. All of these persons were followed through 1951 except 54 who died prior to 1951 and 11 who became lost. The clinical status of each person at the time of diagnosis was assessed on the basis of roentgenographic and bacteriologic data collected during the first six months following diagnosis. Two hundred and eleven persons (78 per cent) were considered to have active tuberculosis at the time of diagnosis according to the *Diagnostic Standards* (1940 edition) published by the National Tuberculosis Association (NTA). Fifty-eight persons (22 per cent) were considered to have arrested disease. This percentage compares quite closely with the 21 per cent incidence of arrested disease found by Puffer, Stewart, and Gass (3) in a group of moderately advanced cases collected in a similar manner.

*Moderately advanced active tuberculosis:* Of the 211 persons considered to have active disease at diagnosis, only 14 failed to have acid-fast bacilli demonstrated in their sputum during the first six months of observation.

Among the persons with active disease 3 nonwhite and 208 white persons were included. The frequency of complicating disease was rather low: diabetes—4 cases; severe rheumatoid arthritis—1 case.

There were fewer females (94 patients) than males (117 patients). In figure 1 the distribution of the patients by sex and age at the time of diagnosis is shown. Whereas there were approximately equal numbers of males and females less than forty years of age in each decennial age group, there were two and a half times as many males as females more than forty. A similar excess of males in the older age groups was seen in a study of far advanced tuberculosis (2) but was not seen in minimal tuberculosis (1).

In figure 2 is shown the number of diagnoses of moderately advanced active tuberculosis made during each calendar year of study. Although the year to year fluctuation was somewhat erratic, there was a significant decrease in incidence during the eleven-year period.

In table 1 is shown the median age at diagnosis of persons admitted to study during the years 1938–1942 and 1943–1948. There was an equal rise in the median age of both males and females admitted during the latter period.

The number of persons whose symptomatic onset preceded diagnosis by a stated interval of time is shown in table 2. The great majority of persons did have symptoms, although generally these did not appear to be so severe as the symptoms associated with far advanced tuberculosis. In keeping with this impression is the fact that diagnoses made in mass surveys accounted for 10 per cent of the total in the present study and only 3.6 per cent of the total in the study of far advanced tuberculosis. It is evident from table 2 that older patients

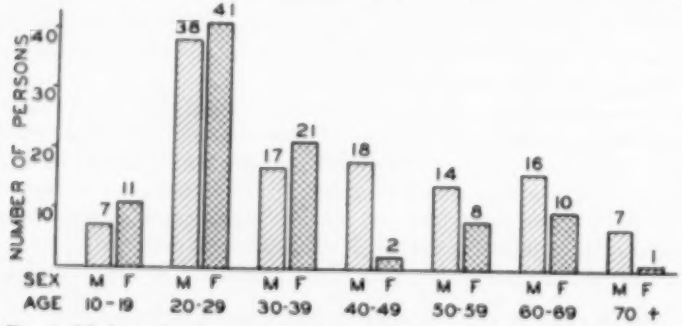


FIG. 1. Moderately advanced active tuberculosis: sex and age at diagnosis

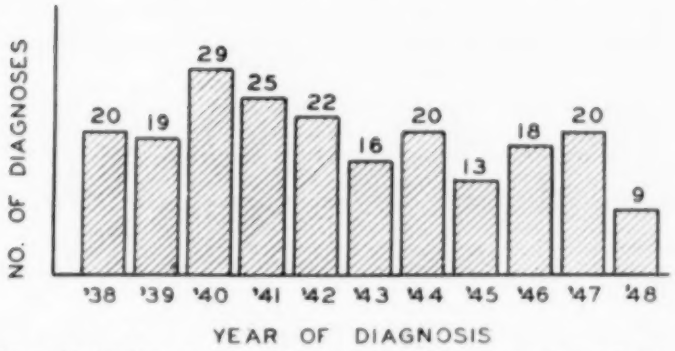


FIG. 2. Moderately advanced active tuberculosis: annual number of diagnoses

TABLE 1

MEDIAN AGE AT DIAGNOSIS OF MALES AND FEMALES DURING YEARS 1938–1942 AND 1943–1948

| | Entire Period 1938–1948 | 1938–1942 | 1943–1948 |
|---|---|---|---|
| Both sexes | 33 years (211)* | 29 years (115) | 34.5 years (96) |
| Males | 38 years (117) | 37 years (62) | 41 years (55) |
| Females | 28 years (94) | 26 years (53) | 29 years (41) |

* Number of persons shown in parentheses.

TABLE 2

DURATION OF SYMPTOMS PRIOR TO DIAGNOSIS ACCORDING TO AGE OF PATIENT

| Age of Patient | Total | Duration of Symptoms (in Months) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 0-2 | 3-5 | 6-11 | 12-35 | 36+ | Indeterminate | No Symptoms |
| All ages | 211 | 64 | 34 | 24 | 28 | 23 | 14 | 24 |
| Less than 35 years | 116 | 46 | 20 | 13 | 13 | 5 | 3 | 16 |
| 35 years and older | 95 | 18 | 14 | 11 | 15 | 18 | 11 | 8 |
| *Percentages* | | | | | | | | |
| All ages | 100.0 | 30.3 | 16.1 | 11.4 | 13.3 | 10.9 | 6.6 | 11.4 |
| Less than 35 years | 100.0 | 39.7 | 17.2 | 11.2 | 11.2 | 4.3 | 2.6 | 13.8 |
| 35 years and older | 100.0 | 18.9 | 14.7 | 11.6 | 15.8 | 18.9 | 11.6 | 8.4 |

tend to have longer periods of symptoms before the establishment of diagnosis than younger patients. It is of interest that persons less than thirty-five years of age with moderately advanced tuberculosis tend to have a shorter duration of symptoms before diagnosis than similarly aged persons with far advanced tuberculosis.

The median duration of symptoms prior to diagnosis was five months for the entire group

TABLE 3

PATIENTS WITH MODERATELY ADVANCED TUBERCULOSIS CLASSIFIED BY STATUS AT ANNIVERSARIES OF DIAGNOSIS

| (1) | (2) | (3) | (4) | (5) | (6) | (7) | (8) | (9) | (10) | (11) | (12) | (13) | (14) | (15) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Anniversary | Living at Anniversary | | | Since Previous Anniversary | | Total | Incomplete Lost | Factors | | Expected Percentages | | | | |
| | Arrested | Active Never Arrested | Active by Relapse | Died Tuberculosis | Died Other Cause | | | Provisional | Correction | Arrested | Active Never Arrested | Active by Relapse | Died Tuberculosis | Died Other Cause |
| 0 | 0 | 211 | 0 | 0 | 0 | 211 | 0 | 1.0000 | 0.4739 | 0.0 | 100.0 | 0.0 | 0 | 0 |
| | | | | | | | | | | | | | *0* | *0* |
| 1 | 7 | 193 | 0 | 9 | 2 | 211 | 0 | 1.0000 | 0.4739 | 3.3 | 91.5 | 0.0 | 4.3 | 0.9 |
| | | | | | | | | | | | | | *4.3* | *0.9* |
| 2 | 83 | 103 | 2 | 9 | 1 | 198 | 2 | 1.0101 | 0.4787 | 39.7 | 49.3 | 1.0 | 4.3 | 0.5 |
| | | | | | | | | | | | | | *8.6* | *1.4* |
| 3 | 99 | 74 | 5 | 4 | 2 | 184 | 4 | 1.0217 | 0.4891 | 48.4 | 36.2 | 2.4 | 2.0 | 1.0 |
| | | | | | | | | | | | | | *10.6* | *2.4* |
| 4 | 111 | 46 | 7 | 3 | 0 | 167 | 11 | 1.0659 | 0.5213 | 57.9 | 24.0 | 3.6 | 1.6 | 0 |
| | | | | | | | | | | | | | *12.2* | *2.4* |
| 5 | 100 | 29 | 9 | 5 | 3 | 146 | 18 | 1.1233 | 0.5856 | 58.6 | 16.9 | 5.3 | 2.9 | 1.7 |
| | | | | | | | | | | | | | *15.1* | *4.1* |
| 6 | 80 | 20 | 7 | 5 | 2 | 123 | 15 | 1.1220 | 0.6570 | 58.5 | 13.1 | 4.6 | 3.3 | 1.3 |
| | | | | | | | | | | | | | *18.4* | *5.4* |
| 7 | 85 | 9 | 8 | 0 | 4 | 106 | 10 | 1.0943 | 0.7190 | 61.1 | 6.4 | 5.8 | 0 | 2.9 |
| | | | | | | | | | | | | | *18.4* | *8.3* |
| 8 | 71 | 6 | 8 | 1 | 0 | 86 | 16 | 1.1860 | 0.8527 | 60.5 | 5.1 | 6.8 | 0.9 | 0 |
| | | | | | | | | | | | | | *19.3* | *8.3* |
| 9 | 60 | 4 | 8 | 1 | 1 | 74 | 11 | 1.1486 | 0.9794 | 58.8 | 3.9 | 7.8 | 1.0 | 1.0 |
| | | | | | | | | | | | | | *20.3* | *9.3* |
| 10 | 50 | 3 | 4 | 1 | 1 | 59 | 13 | 1.2203 | 1.1951 | 59.7 | 3.6 | 4.8 | 1.2 | 1.2 |
| | | | | | | | | | | | | | *21.5* | *10.5* |

(1) Number of years after diagnosis.
(2) Number of living persons with arrested disease at anniversary of diagnosis.
(3) Number of living persons with active disease at anniversary whose disease never attained the arrested status.
(4) Number of living persons at anniversary with active disease because of relapse.
(5) Number who died of tuberculosis since previous anniversary.
(6) Number who died of other causes since previous anniversary.
(7) Total number at anniversary, sum of columns (2) to (6), inclusive.
(8) Number of "incomplete" and lost persons at anniversary.
(9) Provisional factor for anniversary $= \frac{\text{column (7)} + \text{column (8)}}{\text{column (7)}}$.

(10) Correction factor for anniversary = column (9) × correction factor for previous anniversary. The correction factor for anniversary 0 is 100/211 = 0.4739.
(11) Expected percentage of persons with arrested disease at anniversary: column (2) × column (10).
(12) Expected percentage of persons with active disease at anniversary whose disease never attained the arrested status: column (3) × column (10).
(13) Expected percentage of persons at anniversary with active disease because of relapse: column (4) × column (10).
(14) Expected percentage of persons who died of tuberculosis since previous anniversary: column (5) × column (10). Cumulative percentage in italics.
(15) Expected percentage of persons who died of other causes since previous anniversary: column (6) × column (10). Cumulative percentage in italics.

of patients and was five months also for each of the subgroups admitted during the years 1938–1942 and 1943–1948.

*Method:* At the time of diagnosis and at successive anniversaries each patient was assigned a clinical status on the basis of information obtained from the medical record (*see* table 3). Details of the classification and handling of the data have been given previously (4). In table 3 and figure 3 are shown the percentages of persons with one or another status (arrested, active, dead) to be expected at each anniversary, it being assumed that the experience of those with incomplete follow-up will parallel the experience of the persons actually under observation. During the period of study, 11 persons became untraced and hence were not available for subsequent examination.

## RESULTS

### *Over-All Outcome*

After the first anniversary there was a rapid decrease in the percentage of patients with active disease, but the amount of decrease grew less at each succeeding anniversary. Hence, from the seventh anniversary onward a constant proportion (approximately one-tenth) of the original group had active tuberculosis.

From the second anniversary onward there was a slow increase in the percentage of patients with active disease due to relapse, and during the later anniversaries these comprised one-half of the patients with active disease.

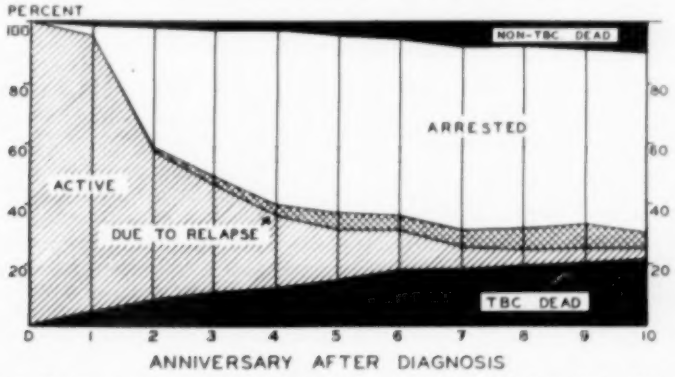


FIG. 3. Status at anniversary. Moderately advanced active tuberculosis: 211 cases

The percentage of patients with arrested disease increased rapidly during the second year following diagnosis. Thereafter the rate of increase slowed abruptly so that, from the fourth anniversary onward, a constant proportion (approximately three-fifths) of the patients had arrested tuberculosis.

Deaths from tuberculosis occurred quite regularly until the seventh anniversary, but were only sporadic thereafter. Up to January 1, 1952, the total number of deaths from all causes among the 211 persons under study was 54, which significantly exceeded the expected mortality[2] of 13.2.

Comparison of figure 3 with the corresponding graph for active minimal tuberculosis (*see* figure 5, reference (1)) reveals a general similarity. Generally speaking, the two graphs might well be duplicates were it not for certain differences which occurred in the follow-up experience during the first two years after diagnosis. In moderately advanced tuberculosis the sharp decrease in the percentage of persons with active disease occurred *after* the first anniversary of diagnosis, whereas in minimal tuberculosis the decrease was already rapid by the time the first anniversary was reached. In moderately advanced tuberculosis the mortality during the first and second years following diagnosis was significantly higher than in active minimal disease.

Incidentally, in moderately advanced tuberculosis there was an appreciable mortality from nontuberculous causes which was not seen in active minimal tuberculosis. This is readily explained by the greater proportion of middle-aged and older persons in the group with moderately advanced disease.

In table 4 are shown the relapse and remission rates for patients with moderately advanced tuberculosis who were under observation for a stated number of years. The relapse rates are in the same range and follow the same downward trend as the rates observed in active minimal tuberculosis. The same is true of the remission rates. It should be noted, however, that, whereas one-quarter of the patients with active minimal tuberculosis attain the arrested status at the first anniversary of diagnosis, only one-thirtieth of the persons with moderately advanced disease do so. Hence, if remission rates for one year of observation were calculable[3], the first-year rate for minimal tuberculosis would undoubtedly be much higher than the first-year rate for moderately advanced tuberculosis.

### *Factors Influencing the Clinical Course*

As four-fifths of the deaths from tuberculosis expected during the ten years following diagnosis occurred before the sixth anniversary, the six-year case fatality from tuberculosis was adopted as an index of clinical outcome.

The presence of cavity is generally considered to have an unfavorable prognostic significance in pulmonary tuberculosis, even when cavity is associated

[2] The expected mortality was calculated as follows: (a) The consecutive years of age in which each person was at risk of death during the study period were tabulated. (b) For each year of age, the number of years at risk was summed up for the group of persons under study. (c) Age-specific mortality rates were applied, using the United States Life Tables and Actuarial Tables 1939–1941.

[3] See reference (1) for a discussion of this problem.

TABLE 4

RELAPSE AND REMISSION RATES* AMONG PATIENTS WITH MODERATELY ADVANCED ACTIVE TUBERCULOSIS AT DIAGNOSIS

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Relapse Rates* | | | | | | | |
| Number of years of observation | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| Number of patients with arrested disease at beginning of year | 139 | 116 | 94 | 72 | 64 | 52 | 37 |
| Number of relapses during year | 9 | 8 | 2 | 2 | 2 | 2 | 0 |
| Relapse rate (in per cent) | 6.5 | 6.9 | 2.1 | 2.8 | 3.1 | 3.8 | 0 |
| Relapse rate among 101 patients with active minimal tuberculosis | 5.0 | 5.9 | 7.5 | 3.4 | 0 | 0 | 0 |
| *Remission Rates* | | | | | | | |
| Number of years of observation | 2 | 3 | 4 | 5 | 6 | | |
| Number of patients with active disease at beginning of year | 188 | 97 | 68 | 35 | 25 | | |
| Number of remissions during year | 85 | 23 | 22 | 6 | 5 | | |
| Remission rate (in per cent) | 45.2 | 23.7 | 32.4 | 17.1 | 20.0 | | |
| Remission rate among 96 patients with active minimal tuberculosis | 41.7 | 37.0 | 29.6 | 18.8 | 20.0 | | |

* In computing these rates, only initial relapses and remissions are considered. Observation periods of one year or less in length are omitted because of the inherent lack of precision in dating the events "relapse of disease" and "remission of disease" (*see* (1)).

with disease of limited extent—the NTA *Diagnostic Standards* are based in part on this premise.

In the present study 115 patients had no evidence of cavity on the diagnostic chest roentgenogram, while in the remaining 96 the combined diameter of all visible cavities varied from 0.5 to 3.9 cm. The six-year case fatality from tuberculosis was 19 per cent in the group without demonstrable cavity and 18 per cent in the group with cavity. Moreover, there was no significant difference in the six-year case fatalities of the group of patients with cavity 0.5 to 1.9 cm. in diameter and the group with cavity 2.0 to 3.9 cm. in diameter.[4]

Age was found to have a profound influence on the case fatality from tuberculosis. Whereas the 116 persons less than thirty-five years of age at diagnosis had a six-year case fatality of 9.5 per cent, the 95 persons whose ages exceeded thirty-five years had a six-year case fatality of 31.5 per cent. A similar association between age and case fatality was found in a study of far advanced tuberculosis (2). As the ratio of males to females was much higher in the older age group (2.5:1) than in the younger age group (4:5) it is not impossible that a sex-specific difference in the case fatality could have contributed to the higher

[4] The difference between case fatalities was tested for significance at the 5 per cent level by means of the standard error, the variances of the case fatalities being estimated by a formula due to Greenwood (5).

TABLE 5

MODERATELY ADVANCED PULMONARY TUBERCULOSIS: TYPE OF TREATMENT AND RESULTS AT END OF STUDY PERIOD ACCORDING TO AGE AT DIAGNOSIS

| Type of Treatment | Age | Total | Disease Never Arrested | | Disease Attained Arrest | |
|---|---|---|---|---|---|---|
| | | | Died | Active | No Relapse | Relapse |
| Bed rest | Total | 132 | 31 | 21 | 64 | 16 |
| | <35 | 50 | 6 | 3 | 33 | 8 |
| | 35+ | 82 | 25 | 18 | 31 | 8 |
| Collapse* | Total | 79 | 4 | 8 | 58 | 9 |
| | <35 | 66 | 4 | 3 | 50 | 9 |
| | 35+ | 13 | 0 | 5 | 8 | 0 |

* Includes 51 persons treated with artificial pneumothorax, 11 with thoracoplasty, and 17 with both pneumothorax and thoracoplasty.

fatality seen in the older age group. However, in neither age group was there a significant difference[1] between the six-year case fatality of the males and that of the females.

As the group of persons without cavity included a higher proportion of older persons than the group with cavity, it is conceivable that any adverse influence of cavity on the case fatality could have been masked completely by the marked age-specific difference in the case fatality. However, the case fatality of persons who had cavity and who were thirty-five years of age and older was not significantly different from the case fatality of similarly aged persons without cavity. The same was true of persons less than thirty-five years of age. In short, it cannot be inferred from these data that the six-year case fatality from tuberculosis is influenced by either the presence of cavity or the size of the cavity at the time of diagnosis.

In table 5 some pertinent data about treatment are summarized. In general, the older patients received collapse treatment less frequently than the younger patients. Neither the type of treatment received nor the age of the patient at diagnosis appears to have influenced the frequency of relapse. This finding is somewhat at variance with the data of a study of far advanced tuberculosis (2), in which it was found that relapse was less frequent after collapse treatment than after bed rest.

### *Moderately Advanced Arrested Tuberculosis*

The group of persons with tuberculosis considered to be arrested at diagnosis differed in several respects from the group whose disease was initially considered to be active. The median age of the persons with arrested tuberculosis was fifty-two years, fully nineteen years above the median age of the persons with active disease. The group with arrested disease included a greater proportion of males than the group with active disease. The annual incidence of moderately advanced arrested cases showed no change over the eleven-year period 1938–1948 in contrast to a decrease in the annual incidence of the moderately advanced active cases.

Up to January 1, 1952, there were 10 relapses and 3 deaths from tuberculosis among the 58 persons considered to have arrested disease at the time of diagnosis. Eight of the relapses occurred among patients having regular chest roentgenograms and were observed within five years of the date of diagnosis. During the period of study 19 deaths occurred among the group with arrested disease and these exceed the expected mortality of 11.0.


## SUMMARY

During the years 1938–1948, 269 residents of the hospital district were found to have moderately advanced tuberculosis, the disease being classified as active in 211 and arrested in 58. Among the persons with active disease, there was found a significant decrease in the annual incidence of cases; the median age at diagnosis of both males and females increased approximately four years during the period of study; and the median duration of symptoms prior to diagnosis was rather short (five months) and remained unchanged during the study period.

An appraisal of the follow-up data shows that, ten years after the diagnosis of moderately advanced active tuberculosis, three-fifths of the persons so diagnosed could be expected to have arrested tuberculosis, one-tenth to have active disease, one-fifth to have died of tuberculosis, and one-tenth to have died of other causes. There is a striking similarity in the follow-up experience of moderately advanced active tuberculosis and minimal active tuberculosis. Age has a profound influence on the clinical outcome of moderately advanced active tuberculosis, middle-aged and older persons having a six-year case fatality from tuberculosis fully three times that of younger patients.

## SUMARIO

*La Historia Subsecuente de la Tuberculosis Pulmonar: V. Tuberculosis Moderadamente Avanzada*

Durante los años 1938-1948, se descubrió que 269 residentes de un distrito hospitalario tenían tuberculosis moderadamente avanzada, clasificándose la enfermedad como activa en 211 y estacionada en 58. Entre las personas con enfermedad activa, hubo una disminución importante en la incidencia anual de casos; la edad media tanto de los varones como de las mujeres aumentó unos cuatro años durante el período de estudio; y la duración media de los síntomas antes del diagnóstico fué algo corta (5 meses), permaneciendo inalterada durante el período de estudio.

La justipreciación de los datos arrojados por la observación subsiguiente revela que, a los diez años del diagnóstico de tuberculosis activa moderadamente avanzada, cabe esperar que tres quintas partes de las personas así diagnosticadas tengan tuberculosis estacionada, la décima parte tenga enfermedad activa, la quinta parte haya fallecido de tuberculosis y la décima parte haya muerto de otras causas. Existe una notable semejanza en la historia subsecuente de la tuberculosis activa moderadamente avanzada y la tuberculosis activa mínima. La edad ejerce un profundo influjo sobre el desenlace clínico de la tuberculosis activa moderadamente avanzada, mostrando las personas de edad madura o más viejas una morboletalidad por tuberculosis a los seis años plenamente el triple de la de los enfermos más jóvenes.

## RESUME

*Histoire des suites de la tuberculose pulmonaire: V. Tuberculose modérément avancée*

Au cours des années 1938-1948, 269 habitants de la région desservie par l'hôpital de l'endroit ont été trouvés atteintes de tuberculose modérément avancée, l'affection étant

classifiée active dans 211 cas et stabilisée dans 58 cas. Parmi les sujets ayant une tuberculose en activité, il a été observé une réduction de l'incidence annuelle des cas, l'âge moyen pour l'homme et pour la femme n'est élevé d'environ quatre ans pendant la période d'observation; la durée moyenne des symptômes antérieurs au diagnostic était relativement courte (5 mois) et elle n'a pas varié pendant la période d'observation.

L'évaluation des données obtenues pendant la période d'observation montre que, dix ans après le diagnostic de tuberculose modérément avancée, on pouvait prévoir pour ces malades la stabilisation de la tuberculose dans trois cinquième des cas, la tuberculose en activité dans un dixième des cas, le décès par tuberculose dans un cinquième des cas et le décès dû à d'autres causes dans un dixième des cas. Les résultats de la période d'observation montrent qu'il existe un parallélisme frappant entre les cas de tuberculose modérément avancée en activité et ceux de la tuberculose a minima en activité. L'âge exerce une profonde influence sur l'issue clinique des cas dé tuberculose modérément avancée chéz le sujet d'âge moyen óu le vieillard; la mortalité par tuberculose par période de six ans étant largement trois fois plus élevée que chez les patients plus jeunes.

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# ROENTGENOGRAPHIC SIMULATION OF CAVITATION BY CASEOUS MATERIAL IN LUNG LESIONS[1]

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## INTRODUCTION

In the interpretation of chest roentgenograms, it has long been taught that areas of lung tissue consolidated by inflammatory exudate or necrosis are radiopaque and that radiolucency within such areas of radiodensity represents actual excavation (1–4). However, some writers have mentioned that a radiolucency which appears to be "cavitary" on the roentgenogram may actually be a lesion which is filled with solid or liquid material. Referring to pyogenic lung abscess, Sante (5) has stated "the central area of destruction may be visible even before rupture of the abscess cavity." Pagel and Simmonds (6), in discussing tuberculous cavities, quote H. Alexander and agree that "When an area of lung tissue has undergone an acute infiltration, a zone of leukocytic 'precavernous demarcation' is found which may show on a film as a circular outline." Loesch (7), in a study of seven tuberculous cavities, reported two instances in which air-filled cavities were considered to be present by roentgenographic examination. On pathologic examination, however, both lesions were completely filled with caseous material and had no bronchial communication on serial section. He pointed out that such lesions might be easily confused with air-filled cavities and that ill-advised therapy might be given on this basis.

The present writers have frequently noted areas of radiolucency which appeared to be air-filled cavities on chest roentgenograms of patients with pulmonary tuberculosis. Pathologic examination of the resected tissue in many of these cases demonstrated that the lesion was actually solid or liquid-filled. An example of this type of lesion is presented in figure 1.

In lesions of this type, inspissation, filling, or collapse of an air-filled cavity conceivably could occur following the preoperative roentgenogram or even during surgery. To eliminate the possibility that such preoperative or operative changes were responsible for the phenomenon, a study was undertaken comparing the reinflated surgical specimens with the actual pathologic findings. Mechanical collapse of air-filled cavities could be eliminated by comparing measurements of the lesions and radiolucencies on roentgenograms with the measurement of the area of disease on pathologic examination. Any gross collapse of air-filled cavities should result in a decrease in the outside diameter of the lesions.

In addition to attempting to establish the accuracy of this observation, the preoperative roentgenograms were correlated with the roentgenograms of the surgical specimens, and observations were made on the nature of the material which produced the observed radiolucencies.

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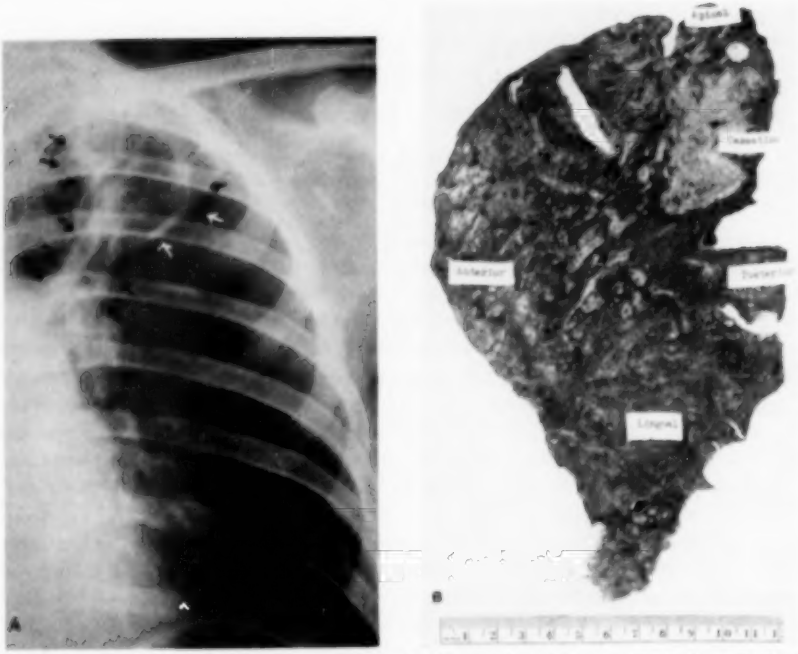

FIG. 1. Striking example of apparent cavitation produced by a solid lesion. Patient was operated upon for a very large radiolucent area, presumably a cavity, in the left apex demonstrated on roentgenogram (*A*) after seven months of chemotherapy. The pathologic specimen (*B*) revealed a large, firm, caseous area that was nonair-containing. Roentgenogram was taken two weeks prior to operation.

## MATERIAL AND METHODS

The series consisted of 11 patients with pulmonary tuberculosis and one with pulmonary coccidioidomycosis. The patients selected for the study had roentgenographic evidence of either residual nodular or cavitary disease, or both, prior to resectional surgery. The patients with tuberculosis had received seven and one-half to nineteen months of preoperative chemotherapy with isoniazid, streptomycin, and para-aminosalicylic acid (PAS) in various multiple-drug regimens. Each resected specimen of pulmonary tissue was inflated by the following technique:

> A glass cannula was tied into the lobar or segmental bronchus and connected by rubber tubing to a gas source. The specimen was then inflated under pressure until it became approximately the size occupied by the specimen in the chest. It was then placed on a cardboard cassette, and a roentgenogram was taken at 10 milliamperes for seven seconds. The kilovolt was varied from 35 to 45, depending on the thickness of the specimen. Multiple views in several planes were obtained by changing the position of the specimen. Inflation was the most satisfactory when complete lobes were used. Although there was often considerable leakage of gas from the raw surfaces of resected segments, a constant state of expansion could be maintained by a rapid flow of gas. Satisfactory roentgenograms could usually be obtained even under these conditions. Following this procedure, the cannula was removed and the specimen was allowed to deflate.

The specimens were examined in the fresh state in 10 instances. Two of the specimens (*Cases 11* and *12*) were inflated with Kaiserling's solution, allowed to fix for one week, and were then examined. The bronchi leading to the area of disease were first opened and examined grossly to determine if any communication with the lesions could be found. The area of disease was then sectioned, and particular attention was paid to the possible causes of the radiolucencies found roentgenographically. Careful measurements were made of the size of the lesions, the size of semi-solid or liquid areas within fibrocaseous nodules, and of any air spaces present. Photographs were made of the dissected gross specimens to document these observations. Sections of the lesions and bronchi were taken for microscopic examination. Smears of the caseous material and tissue sections were appropriately stained for acid-fast bacilli. Aliquots of the tissue were cultured for *M. tuberculosis* in all cases except *Cases 11* and *12*, in which the tissue had been fixed with Kaiserling's solution prior to examination.

The preoperative postero-anterior roentgenograms were reviewed, and the measurements and appearance of the areas of disease were recorded. The roentgenograms of the inflated surgical specimens were similarly examined.

Exact measurement of the size of the lesions found by roentgenography and by tissue examination was difficult, but an attempt was made to quantitate these observations. On the preoperative roentgenogram the extent of the lesion and its appearance were difficult to determine because of loss of definition due to the chest wall and soft tissue densities, pleural reaction, and the use of intensifying screens. Roentgenograms of the inflated surgical specimens had excellent definition, but were complicated by irregularities of expansion due to pleural tears, parenchymal fibrosis, and pleural thickening. Frequently some small areas of atelectasis could not be eliminated by the technique used.

Direct comparisons between roentgenograms and pathologic specimens were made to avoid confusion due to the artifacts mentioned above. Twelve satisfactory comparisons were made out of fourteen attempts. The two failures were due to insufficient inflation of the surgical specimen, which resulted in unsatisfactory roentgenograms.

The 11 cases of tuberculosis were confirmed by either direct smears from caseous foci or by appropriately stained tissue sections which were positive for acid-fast bacilli on microscopy. Tubercle bacilli were cultured from the tissue specimens obtained in *Cases 3*, *9*, and *10*. No cultures had been made in *Cases 11* and *12*, since the specimens were fixed with Kaiserling's solution prior to examination. The remainder of the specimens were negative for *M. tuberculosis* by culture. The diagnosis of coccidioidomycosis in *Case 8* was proved by the presence of spherules containing endospores in the tissue stained with periodic acid-Schiff stain and by a characteristic culture on blood agar media.

## RESULTS

The significant data on the 12 cases are outlined in table 1. The preoperative roentgenograms, the roentgenograms of the inflated surgical specimens, and the pathologic changes found in 4 representative cases are presented in figures 2 to 5, inclusive.

In all of the 12 cases, roentgenographic examination disclosed one or more radiolucencies within otherwise nodular disease. In some instances these radiolucencies were large and in others relatively small. Many would not have been recognized by casual observation, but all were confirmed by multiple roentgenographic views taken at different angles. In addition to the lesions containing radiolucent areas, many nodular lesions also were seen without radiolucency. As

## TABLE 1

PERTINENT DATA ON ELEVEN PATIENTS WITH PULMONARY TUBERCULOSIS AND ONE WITH COCCIDIOIDOMYCOSIS

| Case Number Diagnosis | Surgical Specimen | Length of Preoperative Treatment | Description of Resected Area on Preoperative Roentgenogram | Description of Roentgenogram of Inflated Surgical Specimen | Pathology |
|---|---|---|---|---|---|
| | | *months* | | | |
| 1 Tuberculosis | Right upper lobe | 8 | One day preoperative. An area of scattered disease in right upper lobe 4.5 x 3.5 cm. in diameter. Scattered fine nodules throughout remainder of upper lobe. In the center of area of diffuse infiltration, there were linear densities suggestive of emphysema. No cavity suspected. | Area of infiltration 4.0 x 3.0 cm. containing 3 radiolucent areas 0.7, 0.7, and 0.6 cm. | In posterior segment there was a cluster of caseous nodose lesions surrounded by dense fibrous tissue measuring 4.5 x 4.0 cm. Three discrete liquefied creamy areas 1.1, 0.7, and 0.4 cm. in diameter were present. None contained air. *Microscopic:* The lesions showed caseous areas surrounded by hyalinized connective tissue. No bronchial communication. Culture negative. |
| 2 Tuberculosis | Right upper lobe | 11 | Three weeks preoperative. Area of scattered disease 4.0 x 3.0 cm., containing linear areas of radiolucency. Lesions not dense. Laminagrams 7 weeks preoperative confirmed above. Large nodules and softened areas not suspected. | Area of infiltration 4.3 x 2.5 cm. containing 3 areas of radiolucency 1.6, 1.2, and 1.1 cm. | In apical segment and extending into posterior segment there was a multiloculated nonair-containing necrotic area 4.3 x 2.4 cm. Walls were ragged, and marked fibrosis surrounded these areas. Contained soft yellowish creamy center 1.4 x 0.7, 1.2, and 0.8 cm. *Microscopic:* Walls poorly defined and the center was filled with caseation. No bronchial communication. Culture negative. |
| 3 Tuberculosis | Right upper lobe | 19 | One day preoperative. In extreme right apex a lesion present 3.0 x 2.0 cm., containing 1.8 x 1.3 cm. area of radiolucency. Multiple calcifications present in surrounding tissue and in radiolucency. Calcification in remainder of lung and in hilus. Diffuse infiltration throughout right apex. | Lesion 2.2 x 1.6 cm. with a radiolucent area containing 5 calcified bodies; radiolucent area 1.6 x 1.1 cm. Multiple small areas of calcification in rest of lung and hilus. | In apical segment 2.0 x 2.0 cm. lesion with soft center 1.4 x 0.8 cm. Softened center contained 5 calcified bodies lying loose in a yellowish, creamy substance. Smaller calcified areas were found in the remainder of the lung and hilus. No air present. *Microscopic:* Wall was dense, fibrous tissue surrounding a caseous center and contained areas lined by cuboidal and stratified squamous epithelium. No bronchial communication. Culture positive for tubercle bacilli. |
| 4 Tuberculosis | Left upper lobe, including lingula. | 13 | Three weeks preoperative. Multinodular area of disease 4.5 x 2.0 cm. in size. Lesion was discrete, but had slight diffuse radiolucent areas present. Definition difficult because of pleural reaction. | Multinodular lesion 4.2 x 2.0 cm. containing 2 radiolucent areas 1.8 x 1.7 cm. and 1.0 x 0.4 cm. | Area of infiltration in posterior segment 4.1 x 1.6 cm. with 2 coalescent nodules 2.7 and 1.4 cm. These nodules were yellowish and quite solid and firm. Surrounding areas fibrous. No air present. *Microscopic:* Revealed large areas of caseation with surrounding fibrosis. Some strips of squamous epithelium lined inner aspect of walls. No bronchial communication. Culture negative for tubercle bacilli. |

| | | | | | |
|---|---|---|---|---|---|
| 5<br>Tuberculosis | Right upper lobe | 14 | Three weeks preoperative. In the posterior segment, there was a 2.5 x 2.2 cm. disease area with irregular radiolucent areas centrally occupying a zone 1.8 x 0.8 cm. Emphysema, fibrosis and caseous nodules believed present but not cavitary areas. | One large lesion 2.2 x 2.0 cm. with a radiolucent area 2.0 x 1.5 cm. There was a 2 mm. wall; 2 other lesions present lower down in lobe but not evaluated. | In posterior segment there was a 2.2 x 2.2 cm. lesion with 1-2 mm. fibrous capsule and a moderately firm rubbery and granular center. No air demonstrated. *Microscopic:* Abundant caseous material enclosed in dense fibrous tissue. Inner wall showed respiratory and metaplastic squamous epithelium. Cholesterol and calcium seen in the caseous material. No bronchial communication. Culture negative for tubercle bacilli. |
| 6<br>Tuberculosis | Right upper lobe | 9 | Two days preoperative. Area of disease 3.5 x 2.5 cm. apparently composed of fibrous strands with some areas of radiolucency. Lesion largely radiolucent, but no definite cavity suspected. Other areas of disease seen, but not evaluated. | A lesion seen 3.5 x 2.5 cm. with areas of radiolucency and linear areas scattered throughout. No well-defined cavity was seen as such but rather many areas of radiolucency. | In anterior segment there was a 3.0 x 2.0 cm. area of firm fibrous tissue within which were several closely placed nodules having soft, yellow, creamy centers; largest nodule was 1.6 cm. in diameter and one other was 1.2 cm. in diameter. No air present. *Microscopic:* Dense connective tissue sheets with caseous foci. No bronchial communication. Culture negative for tubercle bacilli. |
| 7<br>Tuberculosis | Right upper lobe | 8 | Three weeks preoperative. Areas of diffuse infiltration 4.5 x 2.5 cm. Lesion not dense and was linear in appearance. Area suggestive of radiolucency 1.0 cm. seen. | A cluster of lesions 3.5 x 2.4 cm. with an area of radiolucency 1.0 x 1.0 cm. | Large part of lesion aseptically removed for storage for chemical analysis, and exact *in situ* measurement not available. Lesion corresponded closely to the roentgenogram and contained softened, yellowish area about 1.0 x 1.0 cm. Lesion was nonair-containing. *Microscopic:* The portion of the necrotic area remaining was composed of a dense, fibrous capsule surrounding masses of caseous material. No bronchial communication. Culture negative for tubercle bacilli. |
| 8<br>Coccidioidomycosis | Left upper lobe | 2<br>(for possible tuberculosis) | Two weeks preoperative. Single lesion 1.5 x 1.5 cm. with a central area of radiolucency 0.9 cm.; definite cavity suspected. | Single lesion 1.6 x 1.7 cm. containing a 1.0 x 0.9 cm. radiolucency. Marked pleural thickening present. | In apical segment a 1.9 x 1.7 cm. lesion, containing small amount of air. Wall sharply demarcated, 2 to 4 mm. in thickness. A 1.0 x 0.8 cm. soft center present composed of yellowish, creamy material. *Microscopic:* The wall is an undulating capsule of connective tissue. Stratified squamous and columnar epithelium present in areas on inner wall. No bronchial communication demonstrated. Culture positive for *Coccidioides immitis*. |

TABLE 1—*Continued*

| Case Number Diagnosis | Surgical Specimen | Length of Preoperative Treatment | Description of Resected Area on Preoperative Roentgenogram | Description of Roentgenogram of Inflated Surgical Specimen | Pathology |
|---|---|---|---|---|---|
| 9 Tuberculosis | Right upper lobe, posterior segment | months 7½ | Two days preoperative. Multinodular lesion 3.0 x 2.0 cm. with definite radiolucent area 0.8 cm. present. Lesion not dense but discrete and easily seen. Laminagrams 6 weeks preoperative confirmed. | Multinodular lesion 2.8 x 2.0 cm. with a 0.7 x 0.7 cm. area of radiolucency centrally. | A multinodular lesion was present in posterior segment 2.8 x 1.6 cm. with a softened, yellowish, central area 0.9 cm. No air was present but a bronchial communication was found. *Microscopic:* Wall composed of dense fibrous tissue with a caseous center. Culture positive for tubercle bacilli. |
| 10 Tuberculosis | Right lower lobe, basilar segments | 7½ | Three weeks preoperative. Lesion in right lower lung field 2.8 x 2.3 cm. with a 2.0 x 1.4 cm. area of radiolucency. | Lesion in posterior basal segment 2.6 x 2.0 cm. containing 2.0 x 1.4 cm. area of radiolucency. Lipiodol in lung and also in lesion. | 2.2 x 2.0 cm. lesion in posterior basal segment filled with yellow, creamy material. Liquid area 1.3 x 0.8 cm. in size. No air, but bronchus opens widely into lesion. *Microscopic:* Lesion had a thick fibrous wall with caseation in the center. Culture positive for tubercle bacilli. |
| 11 Tuberculosis | Right upper lobe | 14 | Four weeks preoperative. Lesion in posterior segment 3.7 x 2.1 cm. with a ring-like radiolucency 2.8 x 1.8 cm. Appeared to be an empty oval cavity. Thoracoplasty done subsequently and lesion was smaller one week preoperatively. | Large lesion 3.5 x 3.2 cm. containing a large area of radiolucency 2.8 x 1.8 cm. Very prominent inner wall. | Area of fibrosis present in posterior segment 3.5 x 3.0 cm. containing a large lesion 2.7 x 2.5 cm. Wall was 1 to 2 mm. in thickness and contained two areas of firm, yellowish caseation along with air. Wide bronchial communication present. *Microscopic:* Dense fibrous tissue wall with central area of caseation. No culture obtained. |
| 12 Tuberculosis | Left upper lobe | 7 | Four weeks preoperative. Had areas of disease in the left apex but lesion under consideration could not be seen definitely on the postero-anterior chest film. | Lesion in anterior segment 1.0 x 0.9 cm. with a 0.6 cm. radiolucent center. Other areas of disease present, but not evaluated because of overlapping and fibrosis. | In anterior segment close to hilus there was a 0.9 x 0.8 cm. lesion with a 1.0 mm. well-defined capsule and a firm yellow center. No air was demonstrated. *Microscopic:* Lesion well-circumscribed with a dense fibrous wall and a center filled with caseous material. No bronchial communication was demonstrated. No culture obtained. |

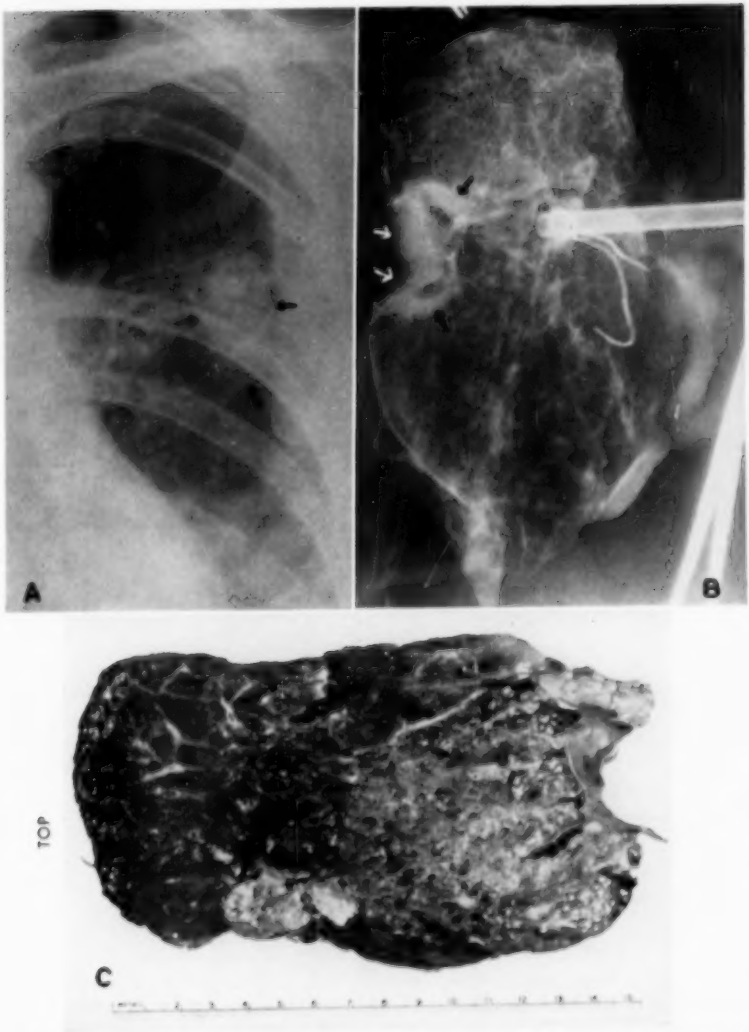


FIG. 2. *Case 4.* Roentgenogram obtained three weeks preoperatively (*A*) reveals a large lesion off the left hilus. Lesion is obscured by the pleural reaction from a previous unsuccessful surgical attempt to resect the lesion. Some questionable areas of radiolucency can be seen but definition is poor. Inflated specimen (*B*) reveals two adjacent lesions, each containing a radiolucency. Overlying the lesion is a lobule of inflated lung due to the fact that the lesions have retracted part of the lobe. The pathologic specimen (*C*) reveals two solid caseous lesions which are nonair-containing and firm. No radiolucency was apparent on the postero-anterior roentgenogram, but was quite definite on the roentgenogram of the inflated specimen.

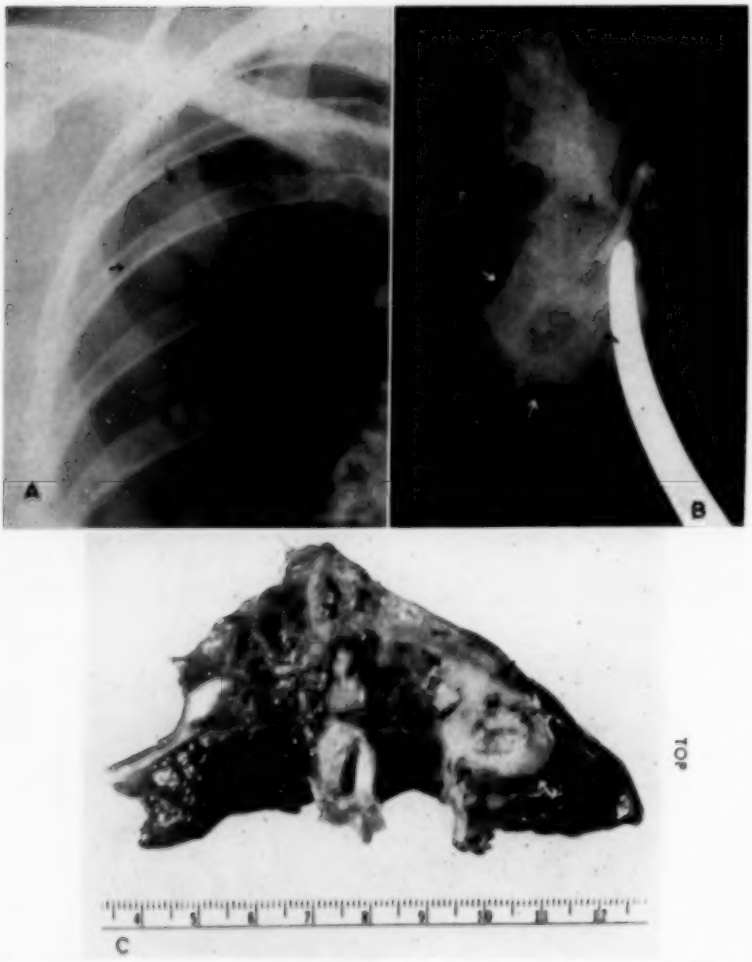


FIG. 3. *Case 9.* Roentgenogram obtained two days preoperatively (*A*) shows the large lesion containing a definite radiolucency. This was well reproduced with better definition on the roentgenogram of the inflated specimen (*B*). The upper part of the segment remained atelectatic, but the lesion could be clearly seen. The small fleck of calcium in the inflated specimen could be faintly identified in the original preoperative roentgenogram. Surgical specimen (*C*) reveals a lesion that is nonair-containing, but had a softened center corresponding in size to the radiolucent area.

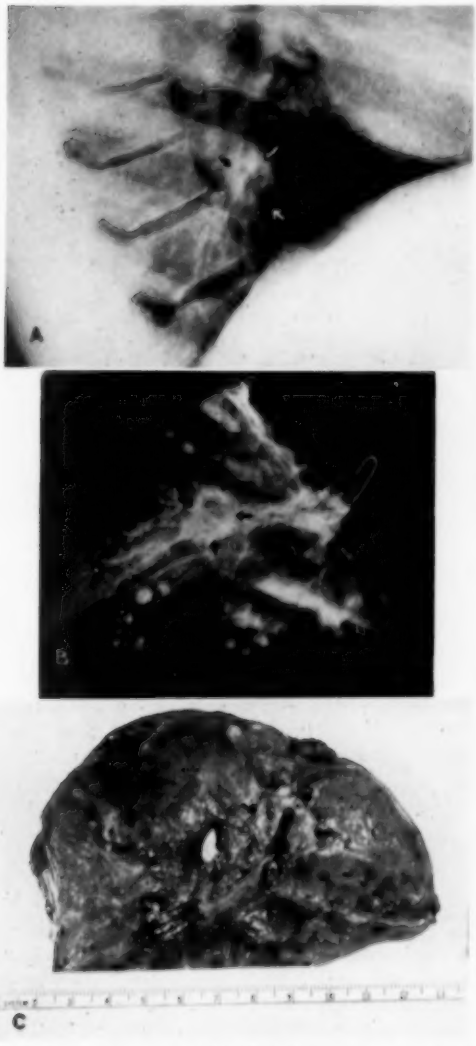


FIG. 4. *Case 10.* Lateral roentgenogram obtained three weeks preoperatively (*A*) reveals lesion in posterior basal segment considered to be an air-filled cavity. Inflated specimen (*B*) is somewhat obscured by the presence of Lipiodol®, but the radiolucent area was well seen. Surgical specimen (*C*) reveals the lesion found. It was nonair-containing and filled with liquid pus which ran out freely. Residual space of abscess can be seen.

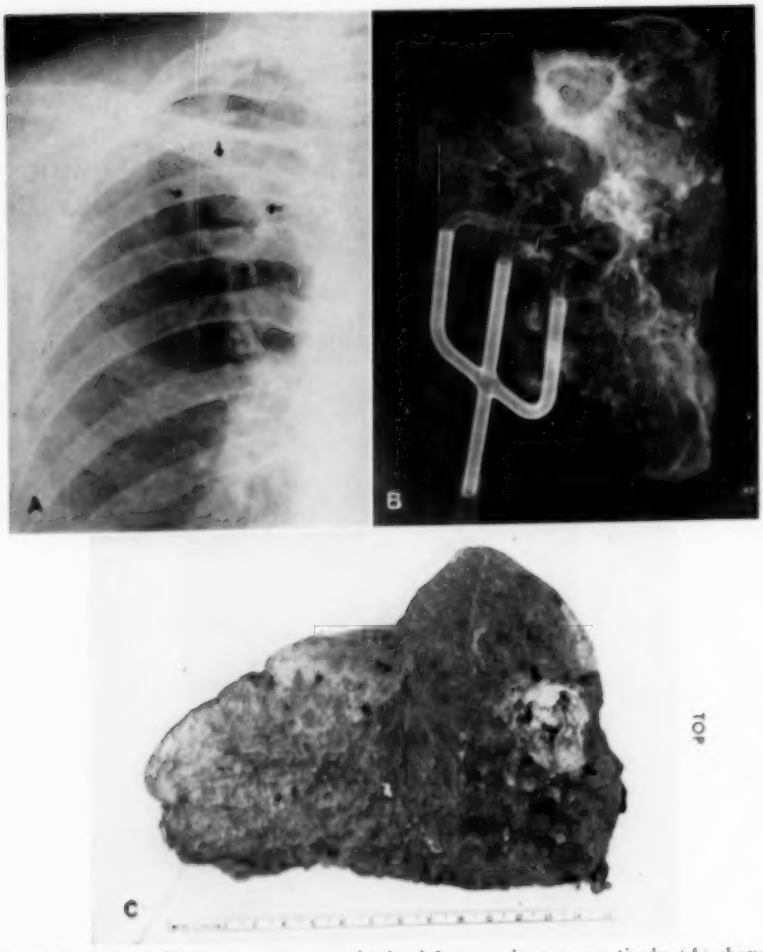


FIG. 5. *Case 11.* The roentgenogram obtained four weeks preoperatively (*A*) shows a radiolucent area in the right upper lobe. A thoracoplasty was performed before resection and obscured the immediate preoperative picture. The roentgenogram of the inflated specimen (*B*) confirms the large radiolucent area seen preoperatively. The surgical specimen (*C*) is very interesting. It had been inflated with Kaiserling's solution and allowed to harden for one week. An air space was present, but it only accounted for a small part of the radiolucent area within the lesion. A large part of the contents was firm caseous material that was radiolucent. No roentgenographic line of demarcation can be seen between the air and caseous material contained in the lesion.

TABLE 2

CORRELATION OF LESIONS AS SEEN ON ROENTGENOGRAM OF THE RESECTED SPECIMEN AND ON PATHOLOGIC EXAMINATION

| Case Number | Size of Single or Multinodular Lesions | | Size of Radiolucencies | |
|---|---|---|---|---|
| | Roentgenogram of Inflated Specimen | Pathologic Examination | Roentgenogram of Inflated Specimen | Pathologic Examination (Material Apparently Producing Radiolucency) |
| | *cm.* | *cm.* | *cm.* | |
| 1 | 4.0 x 3.0 | 4.5 x 4.0 | 0.7, 0.7, and 0.6 | Liquefied caseous material 1.1, 0.7, and 0.4 cm. |
| 2 | 4.3 x 2.5 | 4.3 x 2.4 | 1.6, 1.2, and 1.1 | Softened caseous material 1.4, 0.7, and 1.2 cm. |
| 3 | 2.2 x 1.6 | 2.2 x 2.0 | 1.6 x 1.1 | Softened caseous material 1.4 x 0.8 cm. |
| 4 | 4.2 x 2.0 | 4.1 x 2.0 | 1.8 x 1.7 and 1.0 x 0.4 | Solid caseous nodules 2.7 and 1.4 cm.* |
| 5 | 2.2 x 2.0 | 2.2 x 2.2 | 2.0 x 1.5 | Solid caseous material* |
| 6 | 3.5 x 2.5 | 3.0 x 2.0 | Overlapping areas of radiolucency | Softened caseous material 1.6 and 1.2 cm. |
| 7 | 3.5 x 2.4 | Lesion removed; no exact measurement | 1.0 | Softened caseous material 1.0 cm. |
| 8 | 1.6 x 1.7 | 1.9 x 1.7 | 1.0 x 0.9 | Air and softened caseous material 1.0 x 0.8 cm. |
| 9 | 2.8 x 2.0 | 2.8 x 1.6 | 0.7 | Softened caseous material 0.9 cm. |
| 10 | 2.6 x 2.0 | 2.2 x 2.0 | 2.0 x 1.4 | Liquid caseous material 1.3 x 0.8 cm. |
| 11 | 3.5 x 3.2 | 3.5 x 3.0 | 2.8 x 1.8 | Air and firm caseous material 2.7 x 2.5 cm. |
| 12 | 1.0 x 0.9 | 0.9 x 0.8 | 0.6 | Firm caseous material* |

* Lesions were homogenous throughout, so that the radiolucent areas were similar pathologically to the radiopaque areas.

the problem of apparent cavitation was the major concern, no further analysis was made of these latter lesions.

*Correlation of the Roentgenograms of the Inflated Surgical Specimens with the Pathologic Findings*

In table 2 may be seen a comparison of the size of the lesions and radiolucencies as seen on the inflated surgical specimens and of the size of lesions and material producing the radiolucency on pathologic examination. It may be seen that there was little difference between the gross size of the lesions on the two methods of examination.

In the tissue specimens, air was demonstrated within the lesions from *Cases 8* and *11*, which contained radiolucent areas. *Case 11* is illustrated in figure 5. In both cases it is of interest to note that the lesions contained additional caseous or creamy material which appeared radiolucent along with the contained air.

The actual air content was small in amount and accounted for only a small proportion of the total area of radiolucency. No roentgenographic line of demarcation could be seen between the air and the caseous substance.

In 3 of the specimens, *Cases 4, 5,* and *12,* the area of radiolucency corresponded to lesions composed of solid caseous material. In 7 specimens, *Cases 1, 2, 3, 6, 7, 9,* and *10,* the area of radiolucency apparently corresponded to liquid creamy centers surrounded by a peripheral margin of solid caseous or fibrous material. Most of the lesions had dense fibrous walls, and fibrous tissue was found to be quite radiopaque. Some lesions, however, showed a central radiolucency quite far removed from the fibrous walls; therefore, the surrounding fibrosis is not the sole determining factor for apparent cavitation. In 10 cases it was noted that the area producing radiolucency was yellowish in color, and the liquefied areas were often described as "creamy" in appearance and consistency. Because of the physical appearance of this material, which suggested a high lipid content, Sudan IV stains were performed on two sections. These showed a qualitatively higher fat content in the radiolucent areas, compared with the radiopaque areas.

Bronchial communication with the nodular lesions under discussion was demonstrated in 3 cases (*Cases 9, 10,* and *11*), and epithelium was demonstrated in the lesions in 4 additional ones (*Cases 3, 4, 5,* and *8*), presumably ingrowth from a microscopic but undemonstrated bronchial communication. Serial sections were not made; therefore the presence or absence of microscopic bronchial communication could not be absolutely established.

In general there was a close correlation between disease seen on the roentgenograms of the inflated specimen and that seen on the preoperative roentgenogram, except that the definition observed in the preoperative roentgenogram was not as good as that of the inflated specimen because of technical factors listed previously. In one instance, *Case 12,* the area of disease under consideration could not be well seen on the preoperative roentgenogram. Preoperative roentgenograms of 4 of the cases (*Cases 1, 2, 4,* and *5*) did not show the definite radiolucencies observed in the inflated specimen, due apparently to these same technical factors which reduce definition.

In 2 instances, *Cases 1* and *5,* the postero-anterior roentgenograms were suggestive of localized emphysematous blebs occurring in an area of nodular disease, but this error was dispelled on the roentgenograms of the inflated specimen, in which better definition was available. Radiolucent areas within nodular lesions were seen to account for the appearance of blebs.

## DISCUSSION

The results of this study demonstrate that annular areas roentgenographically suggestive of air-filled cavities may be produced by lesions filled with solid or liquid material. Demonstration of the radiolucent areas on roentgenograms of the reinflated surgical specimen eliminates possible change in the lesion prior to or during surgery. The lack of significant difference in size of lesion as seen by roentgenogram and as found on pathologic examination militates against a collapse of air-filled cavities as a cause for confusion.

The decrease in definition in the preoperative postero-anterior roentgenogram as compared with the roentgenogram of the inflated specimen is not surprising and has been reported by Sweany (8). It was apparently this loss of definition which produced the appearance of emphysema and linear fibrosis in 2 of the cases on the preoperative roentgenogram, as this confusion did not occur on the roentgenogram of the inflated specimen. Although planigrams are of assistance in better recognition of radiolucent areas, it is not believed that they are always of help in differentiating lesions filled with air from those containing fluid or solid material.

An appreciation of this phenomenon is of great importance in the management of pulmonary tuberculosis. In general, air-containing cavities are considered to indicate active disease and are dependent on the interpretation of radiolucent areas on a chest roentgenogram. As many of these areas may represent solid or liquid-filled lesions, such interpretations must be considered in the light of these observations. In addition to simulating cavitation by roentgenogram, these liquid-filled or solid lesions may appear as areas of emphysema or linear fibrosis. In such instances, the amount of residual disease would be underestimated.

If a patient were considered to have an air-filled cavity as a result of erroneous interpretation of these radiolucencies, there are several serious consequences which might result. Such patients might be classified as having either active tuberculosis or the status of a so-called "good chronic" case, with all of the social and epidemologic implications of such classifications. Radiolucencies of this type when present after a period of chemotherapy for tuberculosis might be interpreted as an evidence of failure of the particular therapy employed and thus cause changes in length or type of treatment. Recent methods of evaluation of the efficacy of drug regimens have "cavity closure" as a major criterion. In some instances of apparent failure of cavity closure, the phenomenon herein described may be present.

Unfortunately, there are no reliable roentgenographic criteria by which to distinguish between air-filled cavities and liquid-filled or solid lesions. In general, however, in the present study, the air-filled cavities had a sharp inner line of demarcation between the central radiolucency and the radiopaque wall, were well contrasted from the surrounding disease, and had smooth regular walls. In contrast, the solid lesions had less well-demarcated inner walls, less well-contrasted central radiolucency, and slightly serpentine inner walls.

The incidence of this pseudocavitary type of roentgenographic finding is impossible to determine from the present study. Radiolucencies suggestive of cavitation were present in all 12 of the specimens studied. Nevertheless, it must be remembered that the patients were selected for surgery either on the basis of suggestive cavitation or residual nodular disease following prolonged chemotherapy. It seems likely that these radiolucencies are more common than has previously been appreciated.

The failure to observe this phenomenon more frequently may be due to several factors. Previous pathologic-roentgenographic correlations may have been concerned with advanced disease, so that this observation may have been obscured

by the superposition of multiple lesions on roentgenograms. With the increased frequency of resectional surgery for tuberculosis, more specimens containing single localized lesions are available for study so that the interpretation of roentgenograms can be more precise. In addition, long-term drug therapy in tuberculosis given before surgery may so change the dynamics of the disease that radiolucent material may be found in the lesions more often than previously. The facts that this observation had been made before the use of long-term chemotherapy in tuberculosis and that the phenomenon also occurs in coccidioidomycosis and lung abscess indicate that the increased use of chemotherapy alone is not the major factor. Instead, chemotherapy may have had a secondary effect by producing increased healing of otherwise serious progressive disease.

The cause for the radiolucent appearance of lesions filled with solid or liquid caseous material is unknown as far as can be determined. It is apparently based on a physiochemical difference between two parts of a lesion. The gross appearance of the areas which are radiolucent suggests an increased lipid content as compared with the other areas of disease. In the 2 cases examined by Sudan IV stain, increased amounts of fat were found in the areas which appeared radiolucent. No facilities for quantitative determination of fat content were available as a part of the present study.


## SUMMARY

The pathologic findings on resected pulmonary specimens of 11 patients with tuberculosis and one patient with coccidioidomycosis were correlated with roentgenograms of the inflated surgical specimens and with the preoperative roentgenograms.

In 10 of 11 lung specimens removed surgically from patients with tuberculosis, areas of radiolucency were produced by lesions which were filled with solid or liquid caseous material. These areas simulated cavitation or localized emphysema on standard roentgenograms.

The radiolucent areas may cause serious confusion in regard to the extent and type of disease present by roentgenography.

It is suggested that the development of these areas of radiolucency may result from physiochemical change in caseous or necrotic tissue. This change may be a lipoid type of degeneration and can apparently occur in solid or liquid necrotic material.

## SUMARIO

*Simulación Radiográfica de la Cavitación por las Materias Caseosas de las Lesiones Pulmonares*

Los hallazgos histopatológicos en ejemplares resecados a tuberculosos pulmonares y a un enfermo que tenía coccidioidomicosis pulmonar fueron correlacionados con las radiografías de los ejemplares quirúrgicos inflados y con las radiografías preoperatorias.

En 10 de los 11 ejemplares quirúrgicos de pulmones de tuberculosis, produjeron zonas de radiolucencia lesiones llenadas con materias caseosas sólidas o líquidas. Esas zonas simulaban cavernas o enfisema localizado en las radiografías corrientes.

Las zonas radiolucientes pueden motivar mucha confusión acerca de la extensión y forma de la enfermedad revelada por la radiografía.

Sugiérese que la formación de esas zonas de radiolucencia puede provenir de la alteración fisioquímica del tejido caseoso o esfacelado. Dicha alteración tal vez sea una degeneración de tipo lipoideo y puede al parecer presentarse en materias esfaceladas sólidas o líquidas.

RESUME

*Image cavitaire en radiologie due à la présence de matière caséeuse dans les lésions pulmonaires*

Les résultats de l'examen anatomo-pathologique de pièces de résection, provenant de 11 malades atteints de tuberculose pulmonaire et d'un malade atteint de coccidioidomycose, ont été étudiés par rapport aux radiogrammes de ces pièces réséquées et insufflées et aux radiogrammes pré-opératoires.

Dans 10 cas sur 11 spécimens réséqués chez des tuberculeux, des aires claires étaient produites par des lésions remplies de matière caséeuse solide ou liquide. Sur les radiogrammes standard, ces zones simulaient l'excavation ou un foyer d'emphysème.

Ces aires transparentes aux rayons X peuvent entraîner de graves erreurs, quant à l'étendue et à la forme de l'affection montrées par la radiographie.

Les auteurs suggèrent que la formation de ces aires transparentes aux rayons X pourrait résulter d'une transformation chimio-physiologique survenant dans les tissus caséeux ou nécrosés. Cette transformation pourrait être une dégénérescence de type lipoïdique et il est évident qu'elle peut se produire dans les tissus nécrotiques solides ou liquides.

*Acknowledgment*

The writers are indebted to Major Robert J. Steinborg, M.C., for technical assistance in making the roentgenograms of the reinflated surgical specimens.

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# ANTHRACOSILICOSIS, WITH SPECIAL REFERENCE TO PULMONARY CAVITATION[1]

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(Received for publication May 7, 1953)

## INTRODUCTION

Much has been written in the past on anthracosilicosis, particularly with reference to its roentgenographic and industrial aspects. All of these investigations were conducted outside of the anthracite coal fields and some were made many years ago. Located in the midst of the anthracite coal fields, with a considerable amount of clinical and laboratory material available, the writer has gradually come to realize that his daily experiences were not in agreement with those previously published concepts. Thus, it was considered to be worth while to review the anthracosilicotic problem and to re-evaluate certain aspects in the light of present experience.

This report is a study of 100 patients with anthracosilicosis on whom autopsies were performed during a four-year period ending in 1953. All except 2 of these patients were hospitalized, and the autopsies were performed at the Pottsville Hospital, Pottsville, Pennsylvania, which is the largest hospital in the Pennsylvania southern anthracite coal fields. Dr. R. E. Hobbs, the hospital pathologist, performed the autopsies on all of these patients. A particular interest in undertaking this survey was to determine, if possible, what relationship there was between anthracosilicosis and pulmonary tuberculosis, and especially what part tuberculosis played in the instances of pulmonary cavitation which were encountered.

Some investigators have claimed that there is a close pathogenic alliance between silicosis and tuberculosis and that there is an increased susceptibility to tuberculosis in persons with silicosis (1–3). Pendergrass asserted that it is the presence of associated infection which accounts for most of the disability that arises from silicosis. This infection, when it occurs, may manifest itself in either of two ways: by the development of "tuberculosilicosis" or the development of silicosis with tuberculosis. "Tuberculosilicosis" is claimed to be "a distinct disease entity with certain characteristics peculiarly its own" (3). This alleged interaction of the tubercle bacilli and silica sets up a specific type of granulation tissue (4). In addition to these studies, other investigations nearly always emphasized the close relationship between pulmonary tuberculosis and anthracosilicosis. In particular, the roentgenographic findings in the third stage of anthracosilicosis with cavitation have led many to believe that tuberculosis was also present. Many miners who have been diagnosed tuberculous by this criterion have spent months to years in tuberculosis hospitals.

The present writer's experience with anthracosilicosis, however, which is based on clinical and autopsy findings, was impressive with respect to the lack of

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tuberculous findings in even the most severe cases of cavitation. It was then suspected that some of the older concepts mentioned above might require modification, and this suspicion led to the present review of the 100 autopsied cases of anthracosilicosis.

## OBSERVATIONS

Of the 100 cases of anthracosilicosis, there were only 3 instances of pulmonary tuberculosis; yet there were 15 cases of pulmonary cavitation. None of the latter was apparently due to tuberculosis. The 3 cases of tuberculosis were all of the miliary type; 2 developed in mild cases of anthracosilicosis, and the third occurred in a severe case of anthracosilicosis with cavitation, but the cavitation was nontuberculous.

These 17 cases of anthracosilicosis with pulmonary cavitation are presented in the following case reports, which contain brief clinical and autopsy data pertinent only to the lungs and heart.

In all cases the diagnosis of the presence or absence of tuberculosis was made on the basis of microscopic examination of stained smears from cavity contents and histologic sections. In a few cases, indicated in the case reports, cultures for tubercle bacilli were also obtained.

*Case 1.* M. S., a 38-year-old male, complained of dyspnea, orthopnea, severe hemoptysis, and ankle edema. He had had several admissions for silicosis, but no other significant past medical history. There was no tuberculosis in the family.

### *Clinical and Laboratory Findings*

The patient was a young man, well-nourished, dyspneic, and nonfebrile. The chest revealed scattered rales bilaterally. The heart sounds were rapid and distant. Ankle edema was present.

Several sputum specimens and gastric washings were negative for tubercle bacilli.

On his chest roentgenograms there were confluences of nodulations forming conglomerate masses in the midportion of both lung fields, with a suggestion of an irregular cavity in the central portion of the left lung field. A diagnosis was made of advanced anthracosilicosis with associated infection.

### *Post-Mortem Findings*

The lungs revealed a moderate degree of anthracosilicosis. In the lower lobe of the right lung there was a huge solid mass which cut like rubber. Smaller similar silicotic nodules were scattered throughout the left lung fields.

In the mid-portion of the left lung a cavity was noted, measuring 2 cm. in diameter and filled with puslike material. The smears for acid-fast bacilli were negative. The heart showed marked right ventricular hypertrophy.

The post-mortem diagnosis was anthracosilicosis with apparently nontuberculous cavitation and cor pulmonale.

This patient was the youngest of the group of 18 patients with pulmonary cavitation. The case illustrates how advanced anthracosilicosis with cavitation can develop in a short period of time.

*Case 2.* J. K., a 48-year-old male, complained of dyspnea, cough, and weakness. He lived for only three days in the hospital. The past medical history was noncontributory. There was no tuberculosis in the family.

*Clinical and Laboratory Findings*

The lungs revealed emphysema, wheezes, and dry rales. The heart was slightly enlarged to the left, with frequent premature beats.

Anemia was marked. There were no sputum examinations, nor were any chest roentgenograms obtained.

*Post-Mortem Findings*

The lungs revealed both upper lobes to be almost completely involved with advanced anthracosilicosis, and each lobe contained a solitary cavity 35 mm. in diameter. The cavities were filled with black fluid. Smears were made from both cavities and were negative for acid-fast bacilli. The tissue surrounding the cavity was firm, black, and rubbery. The heart revealed cor pulmonale, no other abnormalities.

The post-mortem diagnosis was anthracosilicosis with apparently nontuberculous cavitation and severe cor pulmonale.

*Case 3.* P. D., a 71-year-old male, complained of cough and dyspnea. He had a massive myocardial infarction, and died in fifteen minutes. The past medical history was unknown. The patient was moribund with pulmonary edema.

There were no laboratory studies or roentgenographic examinations.

*Post-Mortem Findings*

The left lung was edematous and emphysematous and almost completely involved with severe anthracosilicosis. The right lung cut surface was black and rubbery, with a cavity in the lower part of the upper lobe. Smears revealed no acid-fast bacilli. The heart contained a thrombus in the right coronary artery which was recent and extensive.

The post-mortem diagnosis was anthracosilicosis with apparently nontuberculous cavitation and coronary arterial thrombosis with myocardial infarction.

The patients of *Cases 2* and *3* with extensive anthracosilicosis with apparently nontuberculous cavitation died shortly after hospitalization. Once acute cardiac complications develop, these patients have very little cardiopulmonary reserve to help them survive.

*Case 4.* A. G., a 61-year-old male, complained of pain and swelling of the left knee. He had had an infection in the left knee three years prior to admission, and ankylosis was present at the time of admission. The knee had become reinfected. The family history was unknown.

*Clinical and Laboratory Findings*

Examination of the lungs revealed wheezes and dry rales, bilaterally. There was general enlargement of the heart, with no murmurs.

Four sputum examinations were made and one smear was positive for acid-fast bacilli. The two gastric washings were negative for acid-fast bacilli.

On roentgenographic examination, diffuse fibronodulations were noted throughout both lungs. There was a large cavity with a fluid level in the third interspace. The findings were consistent with pneumonoconiosis plus superimposed infection with cavitation.

*Post-Mortem Findings*

The right lung was black, with extensive anthracosilicosis. There was an area of necrosis at approximately the level of the third rib. Small cavities, some with inky fluid, were present. Smears taken from the cavities were all negative for acid-fast bacilli. The heart revealed cor pulmonale. The liver, spleen, and brain revealed areas of extensive miliary nodules which were positive for acid-fast bacilli on microscopy. Miliary nodules were also present

in the lung, but the cavities were apparently nontuberculous. Material obtained from the knee joints revealed numerous acid-fast bacilli on microscopy.

The pathologic diagnosis was: severe anthracosilicosis with apparently nontuberculous cavitation; miliary tuberculosis of lung, liver, and spleen; and cor pulmonale.

This case is an extremely interesting one in that this patient had tuberculous meningitis secondary to a tuberculous arthritis. Although he had mild miliary spread to the lungs, there was extensive anthracosilicosis with a large apparently nontuberculous necrotic cavity.

*Case 5.* L. M., a 60-year-old male, complained of dyspnea and cough. He lived only two days in the hospital, and died of acute heart failure. His past medical history was unrevealing; there was no tuberculosis in the family.

On examination, the lungs revealed emphysema, and rales and wheezes were prominent. There was auricular fibrillation with enlargement of the heart. No laboratory studies or roentgenograms were obtained.

*Post-Mortem Findings*

On post-mortem examination, the lungs revealed numerous large emphysematous blebs and extensive silicosis. In both upper lobes, large cavities were noted which contained inky fluid. There was no evidence of acid-fast bacilli on microscopy of material from the cavities. The heart was tremendously dilated, with hypertrophy of the right ventricle.

The anatomic diagnosis was anthracosilicosis with apparently nontuberculous cavitation and cor pulmonale.

This case of apparently nontuberculous cavitation also illustrates the sudden death which may ensue when patients with cor pulmonale develop cardiac failure.

*Case 6.* J. B., a 68-year-old male, complained of a chronic cough, dyspnea, and weight loss. His past medical history was nonsignificant, and the family history was unknown.

*Clinical and Laboratory Findings*

On examination, the lungs revealed impaired breath sounds, fine crepitant rales, and flatness of the right base. The heart revealed a grade 2 systolic murmur at the base which was transmitted to the mitral area.

Several sputum examinations were negative for acid-fast bacilli.

Roentgenography of the chest revealed fibronodulations in both lungs, with cavitation in the left upper lobe. A smooth mass in the posterior part of the right chest suggested a cyst or endothelioma of the pleura. The remainder was consistent with advanced pneumoconiosis plus superimposed infection and cavitation, most likely tuberculous in origin.

*Post-Mortem Findings*

On post-mortem examination, the lungs were emphysematous. The large cavity apex of the left lung was filled with inky fluid. The surrounding tissue was black and rubbery in consistency. A tumor, 8 cm. in diameter and mostly soft and necrotic, was found in the right lower lobe, occluding the bronchus. The lymph nodes appeared normal. No acid-fast bacilli were seen on microscopic examination. The cells were typical of a squamous-cell bronchogenic carcinoma. The heart revealed cor pulmonale, with normal valves and vessels.

The anatomic diagnosis was anthracosilicosis with apparently nontuberculous cavitation, bronchogenic carcinoma, and cor pulmonale.

This patient with anthracosilicosis with apparently nontuberculosis cavitation also had cor pulmonale plus a large bronchogenic carcinoma.

*Case 7.* G. C., a 66-year-old male, complained of a cough, dyspnea, hemoptysis, and edema. He lived only twenty-four hours in the hospital. For several years he had suffered from cough and dyspnea. The family history was unknown.

There were no sputum or roentgenographic examinations.

*Post-Mortem Findings*

On post-mortem examination, the lungs revealed moderate fibrosis and some atelectasis. The small cavity of the right apex was sectioned histologically and revealed fibrosis with silicosis. No acid-fast bacilli were found on microscopy. The heart was normal.

The anatomic diagnosis was anthracosilicosis with apparently nontuberculous cavitation.

This patient with moderate anthracosilicosis had apparently nontuberculous cavitation in the right apex which could easily have been diagnosed as tuberculous.

*Case 8.* A. B., a 63-year-old male, complained of severe dyspnea, cough, and edema. He had had several hospital admissions for cardiac failure. There was no tuberculosis in the family. On the last hospital admission, the patient lived only twenty-four hours.

*Clinical and Laboratory Findings*

On the admission just prior to the last, the lungs revealed emphysema, grunting expirations, considerable wheezes, and rales. The heart was enlarged to the left, with a grade 1 mitral systolic murmur.

The sputum was negative for acid-fast bacilli.

Roentgenographic examination (three months prior to death) revealed several diffuse fibronodulations throughout both lung fields and emphysema. A large cavity in the right upper lobe involved most of the lobe. There were multiple diaphragmatic adhesions. The cardiac shadow was enlarged in all diameters.

*Post-Mortem Findings*

On post-mortem examination, the lungs revealed a large cavity in the right upper lobe, 8 cm. in diameter and filled with black fluid. Numerous black, rubbery nodules studded both lung fields. There were also small cavities filled with gelatinous material. The remainder of the lung was fibrotic and necrotic. Smear examination of the cavity contents revealed no acid-fast bacilli. The heart was enlarged. The right ventricle was larger than the left and was dilated. The muscle was soft in consistency.

The anatomic diagnosis was anthracosilicosis with apparently nontuberculous cavitation and severe cor pulmonale.

*Case 9.* R. W., a 74-year-old male, complained of dyspnea and cough. He lived only twenty-four hours in the hospital. The past medical history and family history were unknown.

*Clinical and Laboratory Findings*

On examination, the lungs revealed emphysema, wheezes, and rales. The heart revealed a slight systolic murmur at the apex with normal rate and rhythm. There was no enlargement.

No sputum or roentgenographic examinations were made.

*Post-Mortem Findings*

On post-mortem examination, both lungs were black and sectioned hard and rubbery.

Large black nodules were scattered throughout both lung fields. Both upper lobes contained numerous small cavities. Smears and cultures were negative for tubercle bacilli. The right side of the heart was hypertrophied.

The anatomic diagnosis was anthracosilicosis with apparently nontuberculous cavitation and cor pulmonale.

The last two cases (*Cases 8* and *9*) of anthracosilicosis illustrate apparently nontuberculous cavitation and cor pulmonale.

*Case 10.* M. M., a 44-year-old male, died in five hours on the last hospital admission. On a previous admission, five months prior to this, the patient complained of weakness and dyspnea. He was a known diabetic. There was no tuberculosis in the family. The father had died of anthracosilicosis.

*Clinical and Laboratory Findings*

On examination, the lungs revealed an emphysematous chest with diffuse dry rales bilaterally. Except for tachycardia, the heart was normal.

No acid-fast bacilli were found in the sputum. On the previous admission, the blood sugar was 414 mg. per 100 ml.; the blood urea was 78 mg. per 100 ml. The carbon dioxide combining power was 23 volumes per 100 cc.

On roentgenographic examination, diffuse nodulations were noted throughout both lung fields, with adhesions on the dome of the diaphragm. The changes were consistent with the nodular type of silicosis, but the possibility of miliary tuberculosis also had to be considered.

*Post-Mortem Findings*

On post-mortem examination, the lungs were black in color, and the cut surface was extremely rubbery. The upper lobe of the right lung was large, with a hard nodule. The central portion was soft and necrotic. Smears taken from the necrotic cavity revealed no acid-fast bacilli or other organisms. The heart was smaller than normal and markedly atonic.

The anatomic diagnosis was anthracosilicosis with apparently nontuberculous cavitation.

This young man died in a diabetic coma and had extensive anthracosilicosis with apparently nontuberculous cavitation.

*Case 11.* E. H., a 62-year-old male, complained of dyspnea, cough, and ankle edema. The past medical history was not significant. The family history was unknown.

*Clinical and Laboratory Findings*

On examination, the lungs revealed emphysema and bilateral crepitant rales. The heart was enlarged to the left, with auricular fibrillation. There were no murmurs. The liver was enlarged. Pitting edema was present. The right foot was cold and in a pregangrenous state, with absent pulsations.

No sputum examinations were made.

Roentgenographic examination revealed diffuse fibrous changes of both lungs, with an area of increased density of the posterior portion of the left lobe. The cardiac silhouette was enlarged. The findings were consistent with cardiac enlargement, pneumonoconiosis, and pulmonary congestion with small pleural effusion.

*Post-Mortem Findings*

On post-mortem examination, both lungs showed moderately severe anthracosilicosis. The process was more extensive in the left lung, which contained a large anthracosilicotic nodule, measuring 7 by 6 cm. and extending from the hilum to both lobes of the left lung. It was black, rubbery, and contained numerous small cavities varying in size from 5 to 20

mm. The cavities had thin walls and contained inky black fluid. The rest of the lungs showed congestion and edema. Smears from the cavity failed to show acid-fast bacilli or other organisms. The heart was moderately enlarged, and the muscle tone was very poor. The left ventricle was filled with an organized blood clot. The coronary arteries contained fresh thrombi.

The anatomic diagnosis was anthracosilicosis with apparently nontuberculous cavitation and recent coronary arterial thrombosis.

*Case 12.* J. Z., a 76-year-old male, complained of weakness and dyspnea. He was disoriented, and died in three days. He had had an amputation of the penis for a noncancerous lesion at the Jefferson Hospital, Philadelphia, two years prior to the present hospitalization. The family history was unobtainable.

*Clinical and Laboratory Findings*

On examination, the patient was emaciated. The lungs revealed emphysema and bilateral dry crepitant rales. The heart sounds were distant. The rate and rhythm were regular.

No sputum examination was made.

The chest roentgenograms, obtained two years prior to death, revealed extensive fibrotic changes in both lung fields, particularly in the lower halves. Pleural thickening and diaphragmatic adhesions were present.

*Post-Mortem Findings*

On post-mortem examination, the lungs revealed a marked degree of anthracosilicosis bilaterally. The cut surfaces were black and rubbery. Many small cavities were present and were filled with inky black fluid which, on smears, revealed no evidence of acid-fast bacilli or other organisms. The heart revealed a recent thrombosis in a coronary artery.

The anatomic diagnosis was anthracosilicosis with apparently nontuberculous cavitation and a recent thrombosis in a coronary artery.

The patients mentioned in *Cases 11* and *12*, with anthracosilicosis with nontuberculous cavitation, died of myocardial infarction.

*Case 13.* G. C., a 49-year-old male, was admitted to the hospital in severe cardiac failure, and died in six hours. The patient had had previous admissions to this hospital and to the White Haven Sanatorium. There was no tuberculosis in the family.

*Clinical and Laboratory Findings*

The patient had marked pulmonary edema and was moribund. The heart sounds were distant. No acid-fast bacilli were found in the sputum.

On examination, marked nodulations with cavities or emphysematous blebs were found in the upper lobe. The findings were consistent with advanced pneumonoconiosis, emphysema, and superimposed infection of the right upper lobe.

*Post-Mortem Findings*

On post-mortem examination, the lungs revealed a marked degree of anthracosilicosis. In the right upper lobe, small cavities with rigid walls contained black viscid fluid. In the left lobe, nodules were present which, on sectioning, were black and rubbery hard. Many emphysematous blebs were found. The smears for acid-fast bacilli were all negative. The heart was tremendously dilated, with marked hypertrophy of the right ventricle.

The anatomic diagnosis was anthracosilicosis with nontuberculous cavitation and cor pulmonale.

This case was one of extensive anthracosilicosis in a relatively young man who died in heart failure with severe cor pulmonale.

*Case 14.* N. L., a 60-year-old male. An autopsy was performed on this patient in a private mortuary. Little history was obtainable except that he was dyspneic and had had severe emphysema and a history of fractured ribs.

*Post-Mortem Findings*

On post-mortem examination, the lungs were large and black. On sectioning, a large abscess was found in the right upper lobe, 5 cm. in diameter and filled with yellowish-green pus. There was also a smaller cavity, 3 cm. in diameter, filled with clear fluid. The remainder of the lungs showed marked anthracosilicosis with scattered areas of congestion. An inspection was made for fractured ribs. After the removal of the lungs, a small mass was felt in the chest wall which proved to be an abscess of apparently mixed staphylococcal and streptococcal etiology. The heart was normal.

The anatomic diagnosis was anthracosilicosis with apparently nontuberculous cavitation, nontuberculous suppurative abscess, and a normal heart.

This patient had a large nontuberculous abscess in the right upper lobe in addition to the apparently nontuberculous cavitation.

*Case 15.* J. Z., a 54-year-old male. An autopsy was performed on this patient in a private mortuary. He had had a history of cough, marked dyspnea, and edema. The family history was unknown. The physical examination was not recorded.

*Post-Mortem Findings*

On post-mortem examination, the lungs revealed diffuse anthracosilicosis of the left upper lobe. There was a small cavity at the apex. The cavity had smooth thin walls and was filled with watery fluid. The cut surfaces of both lungs were fibrotic; black in areas; and in other areas, blackish red. There were many emphysematous blebs. The smears and cultures from the cavity revealed no tubercle bacilli. Hypertrophy of the right side of the heart was noted.

The anatomic diagnosis was anthracosilicosis with apparently nontuberculous cavitation and cor pulmonale.

This case again illustrates cor pulmonale as a complication of advanced anthracosilicosis with apparently nontuberculous cavitation.

The following are 2 cases of patients with anthracosilicosis who developed miliary tuberculosis involving especially the lungs, liver, and spleen. It should be noted that in only one was the anthracosilicosis at an advanced stage.

*Case 16.* J. K. complained of fever, headache, and weakness. He was dyspneic for two years prior to admission, when he developed an upper respiratory tract infection with cough and fever. The past medical history was negative.

*Clinical and Laboratory Findings*

The patient was extremely ill with scattered rales bilaterally. On examination, the heart sounds were rapid and of poor quality. Examination of the abdomen revealed the liver to be enlarged four fingers below the costal margin.

No sputum examination was made.

Dense, small nodulations were scattered throughout both lungs. The findings were consistent with advanced pneumonoconiosis.

*Post-Mortem Findings*

On post-mortem examination, both lungs were enlarged with a moderate degree of anthracosilicosis. Both lower lobes were entirely consolidated with multiple tubercles. The

smears were positive for acid-fast bacilli. There was no cavitation. Multiple tubercles were found in the spleen. The liver was moderately enlarged and contained tubercles. The heart was normal.

The anatomic diagnosis was anthracosilicosis with miliary tuberculosis involving lungs, liver, and spleen.

*Case 17.* J. S., a 49-year-old male. An autopsy was performed on this patient in a private mortuary. He had died suddenly of coronary arterial thrombosis.

*Post-Mortem Findings*

On post-mortem examination, the lungs were smooth and gray in color. Many pinpoint nodules were scattered diffusely throughout both lung fields. A great deal of normal tissue and a slight degree of anthracosilicosis were noted. There were miliary tubercles in the lungs and spleen. The heart revealed severe atherosclerosis of the coronary arteries, with marked narrowing of the circumflex branch of the left coronary artery. The original focus from which the miliary tuberculosis arose was undetermined.

The anatomic diagnosis was anthracosilicosis with miliary tuberculosis involving lungs and spleen.

## DISCUSSION

The present investigation represents an attempt to re-evaluate the problem of anthracosilicosis and is based upon a survey of 100 autopsied anthracosilicotic patients plus daily observation of many anthracosilicotic miners in all stages of the disease. With this experience, the writer has acquired some concepts which differ from the traditional ones presented in the literature. It must be remembered that a considerable amount of the important literature on anthracosilicosis was published two to three decades ago and all originated in medical centers far from the anthracite coal fields. These concepts have been cited for years with various slight modifications.

The significant source of difference in the present investigation from most of those of the past is the relationship of pulmonary tuberculosis to anthracosilicosis. In the present study, the patients with tuberculosis and the patients with pulmonary cavitation were selected from 100 autopsied cases of anthracosilicosis. The 17 cases specially selected represented the most advanced and severe cases of anthracosilicosis and were thus best suited for this special investigation of the role of tuberculosis.

In the past it was generally believed that these advanced cases of anthracosilicosis with massive confluent densities surrounding chronic cavities were in fact advanced tuberculosis. Moreover, for many years it has generally been accepted that anthracosilicosis usually terminated with pulmonary tuberculosis. Berkelo and Brosius (5) stated categorically that in "third stage silicosis—rapidly enlarging cavities indicate active tuberculosis." It was also believed by some that a certain type of progressive anthracosilicosis was inherently a tuberculosilicosis entity. Finally, in this connection, it was claimed that a great majority of anthracosilicotic patients died with pulmonary tuberculosis.

The results of the present study have shown that, of 100 autopsied patients who had had anthracosilicosis, 15 had cavitation and, of the latter, none had a tuberculous cavity. In addition, histopathologic study of the lungs in all of the 100 cases, which ranged from very mild to severe anthracosilicosis, revealed no

such entity as tuberculosilicosis. The criteria used for the identification of tuberculosis were the histopathology of the lesions and the presence or absence of acid-fast bacilli in the contents of the pulmonary cavities.

In a relatively recent report from the bituminous coal fields, H. A. Slesinger (6) apparently was harboring similar suspicions, for he says "there has been a prevailing impression that most silicotic patients contract tuberculosis. Our clinical and postmortem observations do not corroborate this."

For years it was believed that any extensive silicotic involvement of the apex nearly always meant complicating tuberculosis. The present writer has observed numerous cases of apical silicosis without evidence of tuberculosis. Moreover, Slesinger states that he had encountered a considerable number of cases of anthracosilicosis in which extensive apical fibrosis existed without tuberculosis.

Belt and Ferris (7), studying Welsh coal miners, had several patients examined post mortem who were "suggestive of tuberculosis." Necrosis and even caseation of pulmonary tissue were present without evidence of tubercle bacilli. The writers suggested the term "koniopthisis" for this unusual type of lesion in which they found a mixture of dust reticulation, silicotic fibrosis, and caseation necrosis. They raised a question whether caseation can be produced by silicosis or whether caseation is pathognomonic for tuberculosis. This is a provocative problem, and it is the present writer's belief that caseation necrosis may exist without the presence of tuberculosis.

Interesting case reports have come from the Sea View Hospital in Staten Island, New York, of coal miners with pulmonary cavitation who were hospitalized for tuberculosis but, on autopsy examination, were found to have nontuberculous pulmonary cavitation (8, 9). It is pointed out in this report that tuberculosis is often unjustly suspected as a complicating factor in silicosis.

Gough (10) reported the interesting cases of Welsh coal trimmers in which the chest roentgenograms showed much cavitation superimposed on anthracosilicotic lungs and which were consequently diagnosed as advanced pulmonary tuberculosis. These proved to be nontuberculous pulmonary cavitation at postmortem examination.

Sporadic evidence does exist, therefore, to support the view that extensive cavitation in anthracosilicosis in the vast majority of cases is caused by a nontuberculous process rather than by tuberculosis. It is believed that, if this concept were emphasized to the medical profession, it would be of immense value, not only in the medical management of the patient, but also with respect to economic considerations of both the patient and the publicly supported tuberculosis hospitals.

It is true that, if an anthracosilicotic patient has superimposed tuberculosis, he will usually die of his tuberculosis. Nevertheless, as the bulk of the 100 cases of the present series would have been classified as "tuberculosilicosis" by some clinicians, the findings would be at variance with the statement that "a huge percentage of persons with tuberculosilicosis ultimately dies of tuberculosis." Some of the other causes of death in the present series were ruptured aortic aneurysm, pulmonary embolism, cardiovascular accidents, hypertension, nephri-

tis, cirrhosis of the liver, appendicitis, perforated peptic ulcer, meningitis, accidents, and cancer. The neoplasms involved prostate, liver, stomach, and lung.

It is of interest that there were 5 cases of carcinoma of the lung: 4 were primary and one was metastatic. There have been some unsubstantiated opinions that anthracosilicosis inhibited bronchogenic carcinoma. In the present series, 4 per cent of the patients with anthracosilicosis in all stages of the disease developed bronchogenic carcinoma. The average prevalence of bronchogenic carcinoma in the general male population of the Pottsville Hospital for those four years was 0.23 per cent. It is not the purpose of this report to study the relationship between anthracosilicosis and bronchogenic carcinoma. Nevertheless, an incidence of bronchogenic carcinoma in anthracosilicosis more than ten times that of the general population raises the question whether anthracosilicosis presents an unusually favorable background for cancer of the lung. It is also of interest in this connection to note that in one type of pneumonoconiosis, namely asbestosis, the incidence of bronchogenic carcinoma is also very high. A report by Stoll and associates (11) and a review of cases in the New Haven Hospital by Homburger (12) disclose that between 10 and 15 per cent of people with asbestosis develop carcinoma of the lung. It would not appear unlikely then that the present figures on bronchogenic carcinoma in anthracosilicotics may represent a true increase in incidence elsewhere in the country.

From experience on the clinical service, the impression has been gained that a vast majority of anthracosilicotic patients die with heart disease, namely, cor pulmonale and coronary atherosclerosis. It may be that many years of pulmonary fibrosis induce a more favorable condition for the development of atherosclerosis. Whatever the cause, it is the present writers' clinical impression that these patients with advanced anthracosilicosis usually die a cardiac death and rarely a respiratory death. Slesinger (6) finds also that most deaths he has observed in anthracosilicosis have been due to cor pulmonale.

## SUMMARY

Of 100 autopsied cases of anthracosilicosis, pulmonary tuberculosis was found in only 3 per cent, as judged by the usual histopathologic criteria and examination for acid-fast bacilli on stained smears. All of the 15 patients with pulmonary cavitation had lesions which were nontuberculous.

The majority of the patients died of heart disease, with cor pulmonale accounting for half of the cardiac deaths.

In this series of 100 patients with anthracosilicosis, bronchogenic carcinoma occurred ten times more often than in the general hospital population.

It was not possible to confirm the concept of tuberculosilicosis as proposed by other investigators.

## SUMARIO

*La Antracosilicosis con Referencia Particular a la Tuberculosis Pulmonar*

De 100 casos autopsiados de antracosilicosis, no se descubrió tuberculosis pulmonar mas que 3 por ciento, a juzgar por las habituales pautas histopatológicas y el examen en busca

de bacilos ácidorresistentes en frotes teñidos. Todos los 15 enfermos con cavernas pulmonares tenían lesiones no tuberculosas.

La mayoría de los enfermos fallecieron de cardiopatía, correspondiendo al corazón pulmonar la mitad de las muertas cardíacas.

En esta serie de 100 enfermos de antracosilicosis, el carcinoma broncógeno afecta a los antracosilicoticos a lo menos diez veces más que a la población de un hospital general.

No fué posible confirmar el concepto de la tuberculosilicosis que han propuesto otros investigadores.


## RESUME

*Anthraco-silicose sous l'aspect particulier des lésions cavitaires du poumon*

Parmi 100 cas d'anthrasilicose autopsiés, la tuberculose pulmonaire n'a été découverte que dans 3% seulement des cas, comme il a été démontré par les critères histo-pathologiques usuels et la recherche des bacilles acid-résistants par la coloration sur lames. Chez les 15 malades presentant des cavernes pulmonaires les lésions n'étaient pas tuberculeuses.

La majorité de ces malades sont morts d'une affection cardiaque, le coeur pulmonaire étant responsable des décès dans la moitié des cas ayant succombé à l'affection cardiaque.

Dans cette série de 100 malades atteints d'anthrasilicose, on observe que le cancer bronchiogène survient au moins dix fois plus souvent chez le malade atteint d'anthracosilicose que dans la population hospitalière générale.

Le concept de tuberculose silicose tel qu'il est présenté par d'autres investigateurs n'a pu être confirmé.


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# THE INFLUENCE OF ISONIAZID AND STREPTOMYCIN ON ACID-FASTNESS, TETRAZOLIUM REDUCTION, GROWTH, AND SURVIVAL OF TUBERCLE BACILLI[1, 2]

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## INTRODUCTION

Previous work in this laboratory has demonstrated the usefulness of the triphenyl-tetrazolium chloride reduction test for the determination of the metabolic activity of *Mycobacterium tuberculosis* (1). In a preliminary report it was indicated that isoniazid influences growth and metabolic activity of these organisms in a different way than does streptomycin (2). The finding that isoniazid-treated tubercle bacilli lose their acid-fast staining characteristics (2, 3, 4), while streptomycin-treated bacilli do not, added another tool for the differentiation of the mode of action of the two main therapeutic agents in tuberculosis.

The present investigations had two purposes: The first was to establish whether loss of acid-fastness due to isoniazid depends on the medium and specifically on the presence of Tween® 80. The second was to study the influence of streptomycin and isoniazid on growth, metabolic activity, and acid-fastness of isoniazid-susceptible and isoniazid-resistant tubercle bacilli.

## MATERIAL AND METHODS

To establish the influence of the medium upon the loss of acid-fastness, tubercle bacilli of the H37Rv strain were inoculated into four different media: Dubos Tween®-albumin medium for submerged growth (5); the same medium without Tween®; Proskauer and Beck medium for surface growth (6); and the same medium with the addition of 0.5 ml. of a 10 per cent solution of Tween® 80 per 100 ml. of medium. Each medium in 100 ml. quantities was placed into 250 ml. flasks and was inoculated with 0.1 mg. (wet weight) of tubercle bacilli. Four flasks were used for each medium. After growth became clearly visible, samples were taken from each flask, smeared, and stained by the Ziehl-Neelsen method. Isoniazid (2 $\gamma$ per ml.) was then added, and ten days later another Ziehl-Neelsen stain was done.

The same strain, H37Rv, was used for the experiments correlating growth, metabolic activity, and acid-fastness. To produce isoniazid-resistant bacilli, H37Rv was passed through medium containing increasing amounts of isoniazid. Bacilli were obtained which grew in a medium containing 2 $\gamma$ of isoniazid per ml., while their growth was arrested by 5 $\gamma$ of isoniazid per ml. Test tubes calibrated for nephelometry and containing 10 ml. of Dubos Tween®-albumin medium were inoculated with 0.01 mg. (wet weight) of bacilli per ml., corresponding to 3 nephelometer units (7). Multiplication of the bacilli was followed by nephelometric readings, as described elsewhere (7), and expressed in nephelometer units. To measure one aspect of the metabolic activity of the bacilli, 0.5 ml. of a 2 per cent solution of triphenyl-tetrazolium chloride in phosphate buffer was added to each tube containing 10 ml. of medium. Twenty-four hours later the formazan (reduced tetrazolium) was measured colorimetrically (1). The results were expressed in $\mu$Mols of reduced tetra-

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zolium per ml. of medium. The percentage of nonacid-fast bacilli was estimated in Ziehl-Neelsen stained smears by four observers, and the average was taken as the final result.

The drugs used in all experiments were isoniazid in a concentration of 2 $\gamma$ per ml. of medium and streptomycin in a concentration of 10 $\gamma$ per ml. The drugs were dissolved in saline and sterilized by Seitz-filtration.

## RESULTS

### *Effects of Media on Acid-Fastness of Isoniazid-Susceptible Tubercle Bacilli*

In all four media the tubercle bacilli were acid-fast before exposure to isonazid and became totally nonacid-fast after being exposed for ten days to 2 $\gamma$ of the drug per ml. This occurred in Tween®-albumin medium, in the same medium without Tween® 80 (clumped growth), on Proskauer and Beck medium for surface growth, and in the same medium with the addition of Tween® 80 (for subsurface growth).

### *Correlation of Growth, Tetrazolium Reduction, and Acid-Fastness of Untreated Isoniazid-Susceptible Bacilli*

In ten series, totaling 256 tubes, untreated isoniazid-susceptible bacilli exhibited parallel growth and tetrazolium reduction. In no instance were nonacid-fast bacilli observed in the untreated control series (figure 1).

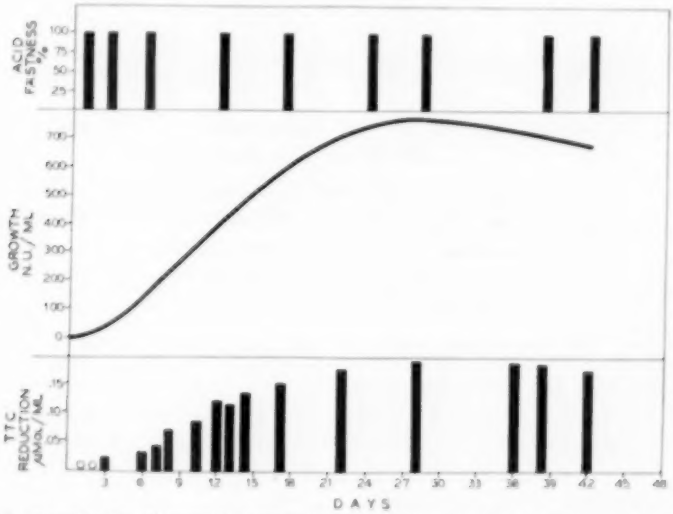


FIG. 1. Correlation of growth, tetrazolium reduction, and acid-fastness of untreated tubercle bacilli (H37Rv).

Acid-fastness is represented in terms of percentage of acid-fast organisms in the upper portion of the graph.

Growth is expressed in terms of nephelometric units (N.U.) per ml. of medium in the center of the graph.

Tetrazolium (TTC) reduction is indicated in $\mu$Mol per ml. by the bars in the lower portion of the graph.

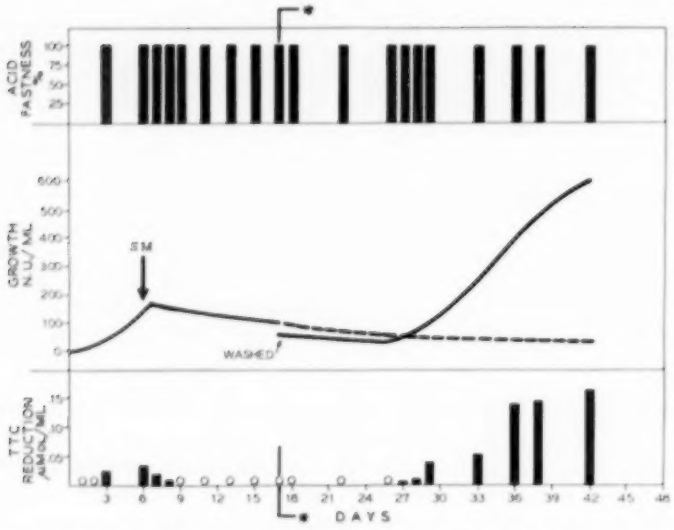


FIG. 2. Correlation of growth, tetrazolium reduction, and acid-fastness of tubercle bacilli (H37Rv) treated with streptomycin and eleven days later resuspended in fresh medium.

The dotted line represents the continuation of the growth curve of the unwashed bacilli.

* The values given hereafter refer to the washed and resuspended bacilli.

### *Influence of Streptomycin on Growth, Tetrazolium Reduction, and Acid-Fastness of Isoniazid-Susceptible Bacilli*

Streptomycin (10 $\gamma$ per ml.) was added on the sixth day after inoculation to six series of cultures comprising a total of 196 tubes. The growth, tetrazolium reduction, and acid-fastness of the bacteria were checked in the same manner as in the control tubes. Growth stopped completely within twenty-four hours, tetrazolium reduction was markedly reduced after twenty-four hours and absent from three days on.

All bacilli treated with streptomycin remained acid-fast throughout the experiment. They did not resume growth as long as they were in contact with streptomycin, but grew out after being washed and resuspended in fresh drug-free medium. This was done in 47 tubes eleven days after exposure to streptomycin; within ten days after resuspension, growth and tetrazolium reduction were resumed in 45 of 47 tubes (figure 2).

The question arose, whether the resumption of growth was due to survival of a few drug-resistant bacilli or to the revival of most bacilli, which had been metabolically dormant after addition of the drug. The fact that no growth occurred in the tubes in which the bacilli remained in contact with streptomycin for forty-five days speaks in favor of resumed growth rather than of the presence of originally streptomycin-resistant bacteria. To confirm this, suspensions of the washed bacilli from 21 streptomycin-treated cultures were diluted $10^{-5}$ times, so

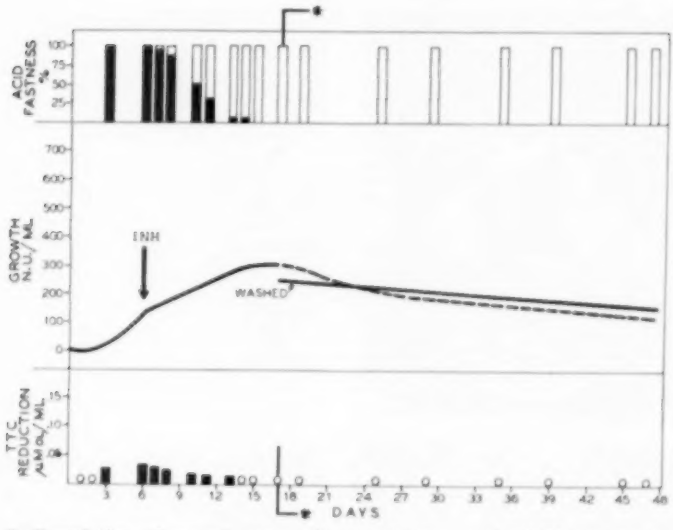


FIG. 3. Correlation of growth, tetrazolium reduction, and acid-fastness of tubercle bacilli (H37Rv) treated with isoniazid and eleven days later resuspended in fresh medium.

The percentage of acid-fast bacilli represented in the upper portion is expressed by the solid black part of the bar.

* The values given from here on refer to the washed and resuspended bacilli.

that only a very small number of bacilli were present in each tube (7). In 83 of 84 tubes, growth occurred after an incubation period of sixteen to twenty-one days. This indicates that most of the bacilli resumed growth.

### *Influence of Isoniazid on Growth, Tetrazolium Reduction, and Acid-Fastness of Untreated Isoniazid-Susceptible Bacilli*

Isoniazid (2 γ per ml.) was added to seven series of cultures with a total of 238 tubes on the sixth day after inoculation. In four of these seven series (figure 3) the growth was slowed for approximately seven days in all 128 tubes. Tetrazolium reduction decreased with the retarded growth rate. Six days after the addition of the drug, however, a small amount was still reduced to formazan, and only after the seventh day, at which time growth had completely ceased, was tetrazolium reduction entirely absent. Under the influence of isoniazid, the tubercle bacilli progressively lost their acid-fast staining properties. An increasing number of rods stained by the counterstain were seen and, at the time when growth and tetrazolium reduction had ceased completely, no acid-fast organisms could be detected in the smears (figure 4). From then on, as long as the bacilli remained in contact with isoniazid, no growth, tetrazolium reduction, or acid-fastness could be detected.

Eleven days after addition of the drug, these nonacid-fast bacilli in 38 tubes were washed and resuspended in drug-free medium. The bacilli remained non-

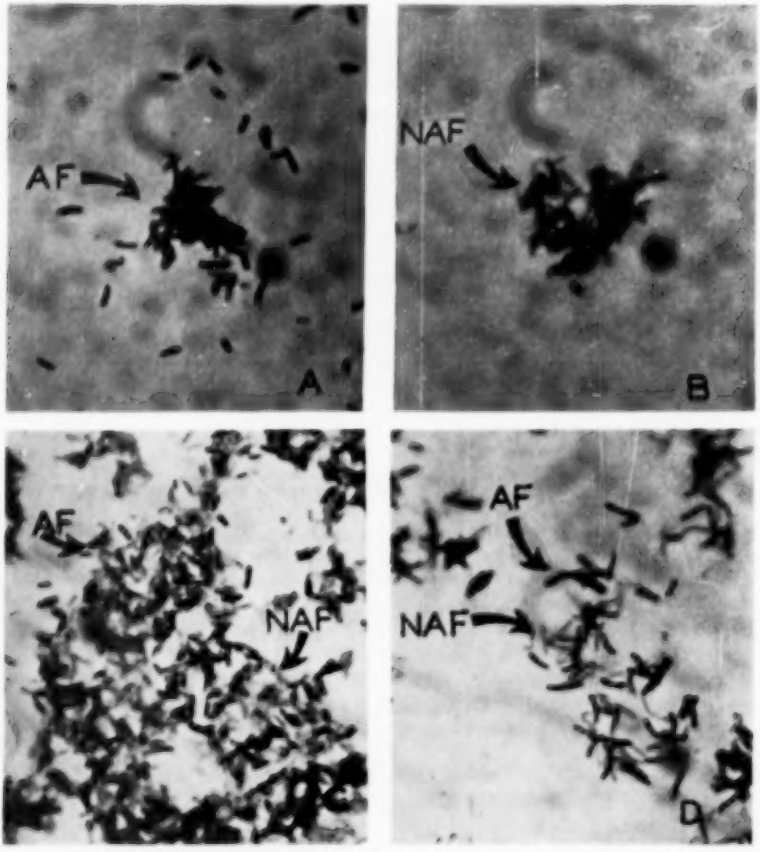


FIG. 4. Tubercle bacilli (H37Rv), Ziehl-Neelsen stain, counterstained with malachite green (× 1,200, green filter). The acid-fast bacilli appear dark, and the nonacid-fast bacilli gray. Many of the nonacid-fast bacilli show marked beading.

*A*. Acid-fast bacilli before the addition of isoniazid

*B*. Nonacid-fast bacilli nine days after the addition of isoniazid

*C*. and *D*. Mixture of acid-fast and nonacid-fast bacilli four and five days after the addition of isoniazid

*AF* = acid-fast bacilli

*NAF* = nonacid-fast bacilli

acid-fast and did not resume growth or tetrazolium reduction. Instead, they underwent a slow process of lysis and clumping.

In all 110 tubes of the three other series, to which isoniazid was added, a different type of result was observed (figure 5). The decrease and final cessation of growth seven days after the addition of the drug seemed identical to that observed in the other isoniazid-treated tubes. Even after the nephelometrically

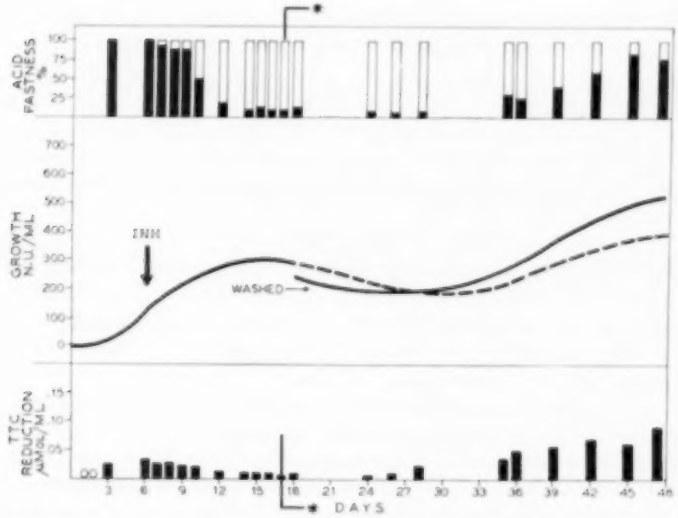


FIG. 5. Correlation of growth, tetrazolium reduction, and acid-fastness of tubercle bacilli (H37Rv) treated with isoniazid and twelve days later resuspended in fresh medium. These bacilli were found to be partially isoniazid-resistant.

* The values given hereafter refer to the washed and resuspended bacilli.

measured growth had ceased, however, a small amount of tetrazolium continued to be reduced and a small percentage of the tubercle bacilli were acid-fast.

Within twenty-six days after the first exposure to isoniazid, growth could be detected again, tetrazolium reduction increased, and an increasing number of acid-fast organisms were seen.

The bacilli in 34 of the tubes were washed and resuspended in fresh medium fourteen days after the addition of the drug. Within ten days, growth in 32 of the tubes was indicated by the nephelometer readings, and there was a parallel increase in tetrazolium reduction and a progressive increase in the percentage of acid-fast bacilli. The bacilli from 6 tubes were tested for isoniazid susceptibility, and were found to be resistant to more than 5 $\gamma$ of isoniazid per ml.

It is important to mention that all of the tubes of each experimental series were inoculated with a suspension of tubercle bacilli obtained from the same tube of stock culture, but that different tubes of stock cultures of the strain H37Rv were used for different experimental series. This may explain why all tubes within a given series gave identical results, while different series, although subjected to the same experimental procedures, varied in their response to the drug exposure.

### *Influence of Streptomycin and Isoniazid on Growth, Tetrazolium Reduction, and Acid-Fastness of Isoniazid-Resistant Bacilli*

Seventy-four tubes of culture medium were inoculated with tubercle bacilli resistant to more than 2 $\gamma$ of isoniazid per ml. Six days after the inoculation,

isoniazid was added to one-third of the tubes, streptomycin to one-third, and one-third was left untreated. The following results were obtained:

> The control cultures and those exposed to isoniazid exhibited identical growth and tetrazolium reduction, and at no time was loss of acid-fast staining properties observed. After streptomycin was added, the isoniazid-resistant bacilli ceased to grow and to reduce tetrazolium in the same manner as was the case with isoniazid-susceptible bacilli. The microorganisms remained acid-fast throughout the experiment.

## DISCUSSION

The findings of the present study indicate that the mode of antituberculous action of isoniazid is quite different from that of streptomycin. While streptomycin stopped the growth of tubercle bacilli almost immediately (figure 2), isoniazid allowed growth to continue in a progressively decreasing fashion for approximately one more generation (8) (figure 3). In a similar way the oxidative utilization of the medium, as measured by tetrazolium reduction, was completely inhibited by streptomycin three days after the addition of the drug, while it required eight days for isoniazid to accomplish the same. The most obvious difference, however, was the complete preservation of the acid-fast staining quality of the streptomycin-inhibited bacilli and the complete loss of acid-fastness of the isoniazid-treated bacilli.

The number of nonacid-fast cells increased with the flattening of the growth curve and with the progressive inability of the bacilli to reduce tetrazolium. When the organisms lost their acid-fast staining characteristics (Ziehl-Neelsen staining method) they consistently ceased to multiply and to reduce tetrazolium. Furthermore, all of the nonacid-fast organisms failed to resume growth and metabolic activity when resuspended in fresh medium.

It seems that under the experimental conditions employed, in which growing tubercle bacilli are submitted to a high concentration of drug, isoniazid is bactericidal and the cell death is associated with the loss of acid-fastness. In contrast, tubercle bacilli maintain their acid-fastness when their multiplication and tetrazolium reduction is rapidly inhibited by a high concentration of streptomycin. Resuspended in fresh medium, the streptomycin-inhibited tubercle bacilli resume growth and metabolic activity. This occurs even after serial dilutions to a point at which, according to calculations (7), only a very small number of organisms is present in each tube. This indicates that the multiplication in fresh medium is not due to a few originally streptomycin-resistant bacilli, but to the resumption of growth by all bacilli which had been metabolically dormant under the influence of the drug. Under the experimental conditions employed, therefore, streptomycin is bacteriostatic. It is not postulated that isoniazid is always bactericidal and streptomycin always bacteriostatic. As Price (9) points out, the same drug under different conditions may be either bactericidal or bacteriostatic. The different conditions can obviously be manifold. They include the growth phase in which the antituberculous drug is added, the number of viable bacilli per ml. of medium, the concentration of the drug in the medium, the composition of the medium, the availability of oxygen, and similar

other factors. Moreover, the conditions listed refer to studies *in vitro*, while *in vivo* the host-infection relationship and other factors influence the mode of action of antituberculous drugs.

It appears significant that, under the influence of a high concentration of isoniazid in the medium, actively growing tubercle bacilli simultaneously lose their capacity for multiplication, their ability to reduce tetrazolium enzymatically, and their acid-fast staining characteristics. Without entering into the discussion of the various theories for the cause of acid-fastness (10, 11, 12, 13) and the difference between structural and chemical acid-fastness (14), it is believed that the tubercle bacilli which have become nonacid-fast under the influence of isoniazid are dead.

This belief is supported by the results obtained in the series represented in figure 4.

> The persistence of a small percentage of acid-fast organisms and of some enzymatic activity indicates the survival of a few bacilli even under the influence of isoniazid. The resumption of growth after washing and resuspension confirms this survival. It is known (3) that, in some cultures, bacilli are present which are naturally resistant to isoniazid. This is corroborated by the finding on the forty-sixth day of the experiment (figure 4), at which time the acid-fast bacilli reappearing in the fresh medium were resistant to a higher concentration of isoniazid than that initially added. Isoniazid fails to influence growth and metabolism of isoniazid-resistant bacilli and does not affect their acid-fastness. The loss of acid-fastness occurs in surface or submerged culture, and does not depend on the presence or absence of Tween® 80.

It is permissible to conclude that the loss of acid-fastness following isoniazid treatment *in vitro* distinguishes the mode of action of this drug from that of streptomycin under the same conditions, and it may represent a reflection of the bactericidal action of isoniazid.

## SUMMARY

Tubercle bacilli exposed to isoniazid *in vitro* under conditions otherwise favorable for growth lose their acid-fast staining characteristics. This loss of acid-fastness is independent of the type of medium or of the presence of Tween® 80. The appearance of nonacid-fast rods in liquid Tween®-albumin medium is gradual and parallels the slowing of the growth rate and the decrease in tetrazolium reduction. Complete loss of acid-fastness, under the experimental conditions described, was uniformly associated with failure of the cells to multiply when transferred to a favorable environment. Frequently, bacilli initially resistant to isoniazid continue to grow, to reduce tetrazolium, and maintain their acid-fastness under exposure to isoniazid.

Streptomycin-treated tubercle bacilli show complete inhibition of growth and tetrazolium reduction almost immediately; nevertheless, their acid-fastness is preserved. Once removed from the influence of streptomycin, they eventually resume growth and the ability to reduce tetrazolium. This indicates that, under experimental conditions employed, streptomycin is bacteriostatic, whereas isoniazid is bactericidal.

## SUMARIO

*El Influjo de la Isoniacida y la Estreptomicina sobre la Acidorresistencia, la Reducción del Tetrazolio, el Crecimiento y la Sobrevivencia de los Bacilos Tuberculosis*

Los bacilos tuberculosos tratados con isoniacida *in vitro* pierden sus caractristicas colorantes ácidorresistentes. Esta pérdida de ácidorresistencia es independiente de la clase del medio y de la presencia de Tween 80. La aparición de bastoncillos anácidorresistentes en el medio líquido de albúmina-Tween es gradual y paralela al retardo del crecimiento y la disminución en la reducción del tetrazolio. La pérdida total de la ácidorresistencia, en las condiciones experimentales descritas, denota muerte bacteriana. Frecuentemente, en los cultivos no tratados, algunos bacilos primitivamente isoniacidorresistentes continúan creciendo, reduciendo el tetrazolio y manteniendo su ácidorresistencia bajo la isoniacidoterapia.

Los bacilos tuberculosos tratados con estreptomicina muestran inhibición total del desarrollo y de la reducción del tetrazolio casi inmediatamente, aunque conservando su ácidorresistencia. Una vez alejados del influjo de la estreptomicina, reanudan con el tiempo el crecimiento y la reducción del tetrazolio. Esto indica, que en estas condiciones experimentales, la estreptomicina es bacteriostática, en tanto que la isoniacida es bactericida.

## RESUME

*L'influence de l'isoniazide et de la streptomycine sur l'acido-résistance, la réduction du tétrazol, la croissance et la survie des bacilles tuberculeux*

Les bacilles tuberculeux traités par l'isoniazide, *in vitro*, perdent leur propriété d'acido-résistance. Cette perte d'acido-résistance est indépendante du type du milieu et de la présence de Tween 80. L'apparition de bâtonnets non acido-résistants dans le milieu liquide Tween-albumine est progressive et parallèle au ralentissement de la vitesse de croissance et à la diminution de la réduction du tétrazol. La perte totale de l'acido-résistance, dans les conditions expérimentales décrites, est le signe de la mort bactérienne. Dans les cultures non traitées, il arrive fréquemment que quelques uns des bacilles initialement acido-résistants continuent à se développer, à réduire le tétrazol et à conserver leur acido-résistance quand ils sont soumis à l'isoniazide.

Les bacilles traités par la streptomycine présentent, presque immédiatement, une complète inhibition de la croissance et de la réduction du tétrazol, tout en conservant leur acido-résistance. Quand ils cessent d'être soumis à l'influence de la streptomycine, ils reprennent plus tard leur développement et léur pouvoir de réduction dú tétrazol. Ces faits montrent que, dans ces conditions expérimentales, la streptomycine est bactériostatique et l'isoniazide, bactéricide.


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# THE EFFECT OF GROWTH FACTOR ON EXPERIMENTAL INFECTION WITH TUBERCLE BACILLI[1]

J. MARKS

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## INTRODUCTION

It has recently been shown that, on plasma agar having a slightly alkaline reaction, tubercle bacilli require a lipid growth factor (1, 2). This lipid, which was originally demonstrated in extracts of tubercle bacilli, is probably identical with mycobactin, the *Mycobacterium johnei* growth factor (3, 4). It is known that the interior of injured cells becomes less acid (5, 6) and, since it is widely accepted that macrophages suffering allergic reactions of the tuberculin type are thereby injured, it appears probable that their intracellular pH rises in consequence. If such an increase in pH could be shown to restrict the multiplication of reinfecting bacilli by leading to an insufficiency of growth factor, it would be possible to relate acquired immunity to allergy in a novel manner. To test this hypothesis, an attempt was made in the work now presented to overcome the resistance to reinfection of guinea pigs immunized with BCG by administering growth factor along with a challenge dose of virulent, human-type, tubercle bacilli.

## MATERIALS AND METHODS

Guinea pigs were immunized six to ten weeks before each experiment by the injection of 0.2 ml. of a well-grown Dubos culture of BCG into the left thigh muscles. Animals were used only if 0.1 ml. of 1:1,000 Old Tuberculin intradermally induced in twenty-four hours an area of erythema and induration 1 cm. or more in diameter. Four separate experiments were undertaken. The method of immunization was the same throughout, but the other procedures used varied and will therefore be described separately for each experiment. Experiment 1 was a preliminary one, and the growth factor used in it was extracted from tubercle bacilli. In the remaining experiments the pure chemical compound mycobactin was used. Tubercle bacilli were always subcultured several times in Dubos medium to obtain well-dispersed growth before use.

### *Extraction of Growth Factor from Tubercle Bacilli*

An ethyl ether extract of 50 gm. (moist weight) of tubercle bacilli killed by steaming was evaporated, and the residual extracted material was suspended in 20 ml. of isotonic saline. The pH of the suspension was brought to 8.0, Tween® 80 was added to give a final concentration of 0.1 per cent, and the mixture was shaken vigorously by hand. The presence of growth factor in this preparation of tuberculolipid was confirmed by cultural tests, but for this preliminary experiment no attempt was made to define its concentration. To provide control lipid material, an ether extract of the yolk of one fowl's egg was evaporated, and the residue was suspended in 60 ml. of 0.1 per cent Tween®-saline.

Sixteen immunized and 12 normal guinea pigs were used in this first experiment. Two groups, one of 4 immunized animals and one of 4 normal animals, were treated with tuberculolipid; two similar groups were treated with egg lipid; and another two were treated with saline. One-half milliliter volumes of lipid suspension or saline were injected into the

[1] From the Central Tuberculosis Laboratory, Cardiff, Wales.

right thigh muscles on the first day of the experiment and also subcutaneously in the right groin on the fourteenth day.

Immediately after the initial injections and a few millimeters from their site, a pair of animals from each group were inoculated intramuscularly with 0.2 ml. of a $10^{-3}$ dilution of a ten-day Dubos culture of the virulent strain of human-type tubercle bacilli, H37Rv. The remaining pairs were similarly infected with 0.2 ml. of a $10^{-2}$ dilution. One animal of each pair was sacrificed after twenty-eight days, and the other after forty-two days.

Two of the 4 immunized animals which were spared reinfection were given tuberculolipid in the manner described, and 2 were given egg lipid in order to detect any effect of these substances on the BCG infection.

At autopsy, an estimate was made of the macroscopic involvement of the right inguinal, femoral, and sublumbar lymph nodes and the spleen, liver, and lungs. In addition, pus or induration was sought in the right thigh muscles. Stained smears were made from material from thigh lesions and enlarged lymph nodes, and the acid-fast bacilli were counted in 200 high-power fields (2 mm. objective).

In the second experiment, growth factor was used in the form of a solution of pure mycobactin in propylene glycol, prepared with the aid of a boiling water bath. The heat and solvent did not appear to affect the growth-promoting property. As controls, a solution in propylene glycol of N stearoyl DL-leucine, a compound with some chemical resemblance to mycobactin but without its growth-promoting effect, and the solvent, propylene glycol, alone were used.

Twenty-four guinea pigs were used, 16 of which were inoculated with strain H37Rv. The experiment consisted of three groups of 4 immunized animals treated with mycobactin, stearoyl-leucine, and propylene glycol, respectively, and one group of 4 normal animals treated with propylene glycol. One animal from each of the four groups was sacrificed thirty-one, thirty-six, forty-one, and forty-six days after infection except for one immunized animal treated with propylene glycol which was lost from intercurrent disease.

Two immunized and 2 normal animals were given mycobactin and two similar pairs were given stearoyl-leucine, but were not infected with strain H37Rv, to detect the effect of these substances and their solvent, propylene glycol, on BCG infection and on normal animals. Mycobactin and stearoyl-leucine were both used as 0.4 per cent solutions, 0.25 ml. being given subcutaneously in the right groin on three occasions, the first, eighth, and nineteenth days of the experiment. A similar schedule was used for animals receiving propylene glycol alone. The challenge dose of H37Rv used was 0.2 ml. of a $10^{-3}$ dilution of a ten-day Dubos culture injected into the right thigh muscles on the first day of the experiment.

Post-mortem examinations were made as in the first experiment except that, in addition, paraffin sections of the viscera were cut and stained with hematoxylin and by the Ziehl-Neelsen method.

Injections of propylene glycol were not well tolerated. Aqueous dilutions employed in later experiments caused less reaction.

Twelve immunized and 4 normal guinea pigs were used in the third experiment. Four immunized animals were each given 0.25 ml. of 0.4 per cent mycobactin in propylene glycol subcutaneously in the right thigh. After twenty-four hours they were inoculated in the same area with 0.1 ml. of a 1:500 dilution of H37Rv culture similar to that used in the previous experiments. At the same time (second day), each animal was given subcutaneously in the right groin a mixture, administered as soon as made, of 0.25 ml. mycobactin solution and 1.25 ml. of a 1:5,000 dilution of the H37Rv culture. The purpose of the latter inoculation was to ensure the intimate contact of growth factor and tubercle bacilli. The 8 other immunized animals were treated similarly except that stearoyl-leucine was substituted for mycobactin in half of them and plain propylene glycol in the rest. The 4 normal animals were infected and treated with plain propylene glycol in the same way to detect any antibacterial effect. A representative of each of the four groups of experimental animals was killed after thirty-two, thirty-four, forty, and forty-one days, and post-mortem examinations similar to those in the second experiment were made.

In the fourth experiment, a different control lipid, palmitoethanolamide, was used which, unlike stearoyl-leucine but like mycobactin, precipitates when its solution in propylene glycol is diluted with saline. Twelve immunized and 4 normal guinea pigs were employed. Six immunized animals were inoculated, both subcutaneously in the right groin with 1.5 ml. and intramuscularly in the right thigh with 1.0 ml. with a mixture, injected as soon as made, of one part of 0.8 per cent mycobactin in propylene glycol and nine parts of a $10^{-3}$ dilution of H37Rv culture. The culture was similar to those used in the previous experiments and was diluted with Dubos medium (casein hydrolysate omitted). The remaining 6 immunized animals were injected similarly, substituting 0.8 per cent palmitoethanolamide in propylene glycol for mycobactin solution, and the 4 normals were also injected, substituting plain propylene glycol. All of the animals were sacrificed forty days after their inoculations and examined as in the second experiment.

## RESULTS

### *First Experiment (Growth Factor Extracted from Tubercle Bacilli)*

Autopsy of the 12 normal (nonimmunized) animals infected with strain H37Rv revealed no difference between any of the experimental groups; all presented the unmodified appearance of virulent tuberculous infection. The findings in the 12 immunized animals similarly infected are shown in table 1.

In the first section, which was comprised of animals with the lighter infection and shorter duration, the animal receiving growth factor (tuberculolipid) had

TABLE 1

THE EFFECT OF CRUDE MYCOBACTERIUM TUBERCULOSIS GROWTH FACTOR ON THE COURSE OF REINFECTION WITH VIRULENT TUBERCLE BACILLI (H37Rv) IN GUINEA PIGS PREVIOUSLY IMMUNIZED WITH BCG

| Drug Administered | Dilution of Infecting Culture | Days Before Sacrifice | Evidence of Tuberculosis at Autopsy | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Site of Inoculation | Lymph Nodes | | | Spleen | Liver |
| | | | | Inguinal | Femoral | Sublumbar | | |
| Saline | $10^{-1}$ | 28 | 0 | 0 | Trace (0) | 0 | 0 | 0 |
| Egg lipid | $10^{-1}$ | 28 | 0 | 0 | ∓ (3) | ∓ (0) | 0 | 0 |
| Growth factor | $10^{-1}$ | 28 | 0 | ∓ (3) | ∓ (8) | ∓ (2) | 0 | 0 |
| Saline | $10^{-2}$ | 28 | ∓ (8) | ∓ (19) | ∓ (200) | ∓ (0) | Trace | 0 |
| Egg lipid | $10^{-2}$ | 28 | + (54) | Trace (0) | ∓ (14) | ∓ (0) | 0 | 0 |
| Growth factor | $10^{-2}$ | 28 | + (5) | + + (9) | ± (2) | ∓ (2) | Trace | 0 |
| Saline | $10^{-3}$ | 42 | ∓ (2) | ∓ (1) | ± (7) | ∓ (0) | ∓ | 0 |
| Egg lipid | $10^{-3}$ | 42 | ± (36) | ∓ (18) | ∓ (12) | ∓ (12) | 0 | 0 |
| Growth factor | $10^{-3}$ | 42 | + (2) | ∓ (0) | ∓ (1) | ∓ (0) | ∓ | 0 |
| Saline | $10^{-4}$ | 42 | ± (48) | + (0) | ± (0) | ± (12) | ∓ | 0 |
| Egg lipid | $10^{-4}$ | 42 | ∓ (12) | ± (12) | ∓ (24) | ± (0) | 0 | 0 |
| Growth factor | $10^{-4}$ | 42 | + (4) | + + (1) | ± (2) | ∓ (1) | ∓ | 0 |

The degree of macroscopic disease is indicated and then, in parentheses, the number of acid-fast bacilli in 200 fields of a stained smear. Films were not made from the viscera or from unaffected lymph nodes or sites of inoculation.

TABLE 2

THE EFFECT OF MYCOBACTIN, N STEAROYL DL-LEUCINE, PALMITOETHANOLAMIDE, AND THE SOLVENT, PROPYLENE GLYCOL, ON THE COURSE OF REINFECTION WITH VIRULENT TUBERCLE BACILLI IN IMMUNIZED GUINEA PIGS

Experiments 2, 3, and 4 Combined

| | Drug Administered | Days Before Sacrifice | Evidence of Tuberculosis at Autopsy* | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Inoculation Site | Lymph Nodes | | | Spleen | Liver |
| | | | | Inguinal | Femoral | Sublumbar | | |
| Experiment 2 | Mycobactin | 31 | 0 | Trace (0) | ∓ (0) | 0 | 0 | 0 |
| | | 36 | 0 | Trace (0) | Trace (0) | ∓ (1) | 0 | 0 |
| | | 41 | 0 | Trace (0) | ∓ (0) | 0 | 0 | 0 |
| | | 46 | 0 | ∓ (0) | ∓ (2) | ∓ (0) | ++ | ∓ |
| | Stearoyl leucine | 31 | 0 | Trace (7) | ∓ (1) | 0 | 0 | 0 |
| | | 36 | 0 | Trace (0) | ∓ (0) | ∓ (0) | 0 | 0 |
| | | 41 | 0 | ± (5) | ± (8) | ∓ (2) | 0 | 0 |
| | | 46 | 0 | Trace (0) | Trace (0) | ∓ (0) | 0 | 0 |
| | Propylene glycol | 31 | 0 | 0 | Trace (0) | 0 | 0 | 0 |
| | | 36 | 0 | Trace (0) | ∓ (1) | Trace (0) | 0 | 0 |
| | | 41 | 0 | 0 | ± (4) | ∓ (8) | 0 | 0 |
| | | Intercurrent death | - | - | - | - | - | - |
| Experiment 3 | Mycobactin | 32 | + (32) | ± (6) | ∓ (3) | ± (3) | 0 | 0 |
| | | 34 | + (3) | ∓ (4) | Trace (0) | ∓ (0) | 0 | 0 |
| | | 40 | + (56) | + (0) | ∓ (0) | ∓ (1) | + | 0 |
| | | 41 | ± (24) | ∓ (3) | ∓ (1) | ∓ (0) | ∓ | 0 |
| | Stearoyl leucine | 32 | 0 | ∓ (0) | ∓ (1) | Trace (0) | 0 | 0 |
| | | 34 | ∓ (7) | 0 | 0 | 0 | 0 | 0 |
| | | 40 | ∓ (5) | ∓ (0) | ∓ (1) | ∓ (0) | 0 | 0 |
| | | 41 | ∓ (3) | 0 | 0 | 0 | 0 | 0 |
| | Propylene glycol | 32 | 0 | ∓ (3) | + (24) | + (0) | 0 | 0 |
| | | 34 | 0 | ∓ (0) | ∓ (0) | 0 | 0 | 0 |
| | | 40 | Trace (1) | ± (6) | ± (0) | ∓ (8) | 0 | 0 |
| | | 41 | 0 | ± (0) | ∓ (0) | ∓ (0) | 0 | 0 |
| Experiment 4 | Mycobactin | 40 | + (24) | ± (1) | ± (0) | ∓ (2) | 0 (0.81) | 0 |
| | | 40 | + (100) | ± (0) | ∓ (0) | ∓ (0) | 0 (0.71) | 0 |
| | | 40 | + (12) | ± (6) | ∓ (0) | ∓ (0) | Trace (0.90) | 0 |
| | | 40 | ± (4) | ∓ (0) | ∓ (0) | Trace (0) | 0 (0.68) | 0 |
| | | 40 | ± (1) | ∓ (0) | ∓ (0) | ∓ (0) | ∓ (0.90) | 0 |
| | Palmitoethanolamide | 40 | + (200) | + (0) | ± (0) | Trace (2) | 0 (0.86) | 0 |
| | | 40 | ∓ (0) | + (0) | + (0) | ∓ (0) | 0 (0.91) | 0 |
| | | 40 | + (2) | + (0) | + (0) | ∓ (1) | 0 (0.84) | 0 |
| | | 40 | + (3) | ± (0) | ∓ (0) | ∓ (0) | 0 (0.73) | 0 |
| | | 40 | + (10) | + (0) | ± (0) | ± (0) | ± (1.30) | 0 |

* See table 1.

The histologic findings are presented in table 3. In the fourth experiment, the weight of the spleen in grams is given.

considerably more tuberculous disease than the controls, but in the remaining sections no such difference was evident. The lipids injected into animals not infected with strain H37Rv induced no reaction other than collections of macrophages at their site.

TABLE 3

HISTOLOGIC EVIDENCE OF TUBERCULOSIS IN THE EXPERIMENTS RECORDED IN TABLE 2

| Guinea Pig Number | Degree of Tuberculous Disease on Microscopy | | | | | |
|---|---|---|---|---|---|---|
| | Spleen | | | Liver | | |
| | Mycobactin Group | Inert Lipid Controls | Solvent Controls | Mycobactin Group | Inert Lipid Controls | Solvent Controls |
| **Experiment 2** | | | | | | |
| 1 | 0 | 0 | 0 | Trace | 0 | 0 |
| 2 | 0 | 0 | 0 | Trace | ± | Trace |
| 3 | 0 | 0 | 0 | 0 | 0 | Trace |
| 4 | ++* | 0 | · | + | 0 | · |
| **Experiment 3** | | | | | | |
| 1 | 0 | 0 | 0 | 0 | ± | ± |
| 2 | 0 | 0 | 0 | 0 | 0 | Trace |
| 3 | ++* | 0 | 0 | + | 0 | Trace |
| 4 | Trace | 0 | Trace | Trace | ± | Trace |
| **Experiment 4** | | | | | | |
| 1 | 0 | 0 | · | ++ | Trace | · |
| 2 | 0 | 0 | · | ++ | + | · |
| 3 | ++* | 0 | · | ++ | Trace | · |
| 4 | 0 | +* | · | ++ | 0 | · |
| 5 | ++* | 0 | · | Trace | Trace | · |

* Acid-fast bacilli demonstrated.

Key to symbols: ++ multiple necrotic lesions; + one necrotic lesion or several large foci with degenerate parenchymal cells and collections of histiocytes; ± one large focus or several small ones.

The average degree of involvement in four sections is recorded.

### *Second Experiment (Mycobactin in Propylene Glycol)*

In the second experiment, pure mycobactin in propylene glycol was used in place of the bacillary extracts. The post-mortem findings in the immunized animals infected with strain H37Rv are presented in tables 2 and 3. There were no macroscopic lesions at the sites of reinfection and no obvious differences in the degree of lymph node involvement between any of the treatment groups. Small aggregations of histiocytes were seen in the livers of some animals in each experimental group but in one case, an animal which received mycobactin, there were large foci of degenerate parenchymatous cells together with histiocytes. The same animal was the only one in this second experiment to show splenic lesions; multiple necrotic areas containing acid-fast bacilli were present.

The normal animals infected with strain H37Rv and treated with propylene glycol presented the unmodified appearance of experimental infection with virulent tubercle bacilli, showing that the solvent for the drugs had no appreciable

action in the dosage used. The normal and immunized animals which were not infected with H37Rv showed no reaction to stearoyl-leucine and only a minor macrophage response to the deposits of mycobactin.

*Third Experiment (Mycobactin and Living Tubercle Bacilli Administered at the Same Site*

In the third experiment, mycobactin and living tubercle bacilli were administered at the same site, both concurrently and with a twenty-four-hour interval. The disease in the normal animals infected with strain H37Rv was apparently unaffected by their treatment with propylene glycol. The autopsy findings in the immunized animals are presented in tables 2 and 3. The mycobactin-treated group had slightly larger lesions at the sites of infection and tubercle bacilli were found somewhat more frequently both in these and in the lymph nodes, as compared with the lipid control and solvent control groups. Macroscopic lesions of the spleen were seen in 2 mycobactin-treated animals, but in none of the controls. Both showed lesions microscopically, which were severe in one case and contained acid-fast bacilli, but were small and non-necrotic in the other. One animal treated with propylene glycol showed a small non-necrotic splenic lesion on microscopy. Microscopic lesions of the liver were found in only 2 mycobactin-treated animals, but in one of them necrosis was present, the only example of liver necrosis met in the third experiment.

*Fourth Experiment (Use of Palmitoethanolamide as Control Lipid)*

The fourth experiment was somewhat similar to the third except for the use of palmitoethanolamide as a control lipid. One mycobactin-treated animal was deleted from the series because at autopsy it was found that its groin inoculation had reached the peritoneal cavity. One control animal was lost from intercurrent infection. The post-mortem findings in the rest of the immunized animals are given in tables 2 and 3. Local lesions were approximately the same in the two experimental groups, but lymph node involvement was slightly greater in the palmitoethanolamide-treated animals. Lesions of the spleen were found in 2 mycobactin-treated animals, and multiple necrotic lesions of the liver were observed in 4. One control animal had splenic lesions, and one had a solitary necrotic liver lesion. Acid-fast bacilli were found in all 3 diseased spleens, but in none of the livers. The nonimmunized infected animals presented unmodified tuberculosis.

No macroscopic lesions of the lung were seen at autopsy in reinfected immunized animals in any of the four experiments. Collections of histiocytes were often found on microscopy in these animals' lungs, but no necroses or tubercles were found. It did not appear practicable to grade the degree of cellular infiltration in different animals.

## DISCUSSION

If the experimental findings in the three experiments with mycobactin are considered together, little difference is evident between the immunized myco-

bactin-treated animals and the controls in terms of degree of lymph node involvement or extent of the lesions at the site of reinfection with a H37Rv strain of tubercle bacilli. Definite lesions of the spleen with demonstrable acid-fast bacilli were found in 4 of the 13 mycobactin-treated animals, however, and in only one of 20 controls (13 lipid controls and 7 solvent controls). Moreover, severe liver lesions (grade two-plus or plus) were found in 6 of the mycobactin-treated animals, but in only one control. Nevertheless, the aid given by mycobactin to virulent reinfecting bacilli in the immunized animals was hardly striking enough to support the hypothesis that availability of growth factor plays an important part in acquired immunity. As mycobactin in the form administered appeared largely to be deposited at the site of injection, it is likely that the experimental methods chosen for the present work were not ideal for demonstrating its activity *in vivo*. The partial effect observed does, therefore, encourage the hope that a method may be found to associate the growth factor and reinfecting bacilli more closely in the experimental animal.

*Acknowledgments*

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# *Case Reports*

## VASCULAR ANOMALIES ASSOCIATED WITH INTRAPULMONARY BRONCHIAL CYSTS[1]

WILSON WEISEL, JOHN W. DOCKSEY, AND MARVIN GLICKLICH

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### INTRODUCTION

The serious technical hazards created by anomalous blood vessels in resectional surgery of the lung and the frequent association of major vascular anomalies with intrapulmonary bronchial cysts have occasioned this report of 5 cases in which vascular anomalies were prominent. The cases have been of particular interest because of the diagnostic difficulties which they presented.

As the literature concerning intrathoracic vascular anomalies has been thoroughly reviewed (1–5) and the theories of origin (6–8), clinical course, and surgical significance have been summarized (9–12), no further review of the literature is included in the present report. Instead, an attempt has been made to describe the vascular abnormality in detail and to point out the features which seem important for preoperative and operative recognition of these anomalies.

### CASE REPORTS

*Case 1* (E. R. T.; No. 126-623). A 25-year-old white male was admitted to the hospital on June 1, 1950, with the complaints of productive cough, right chest pain, fever, and chills of two weeks' duration. A review of his history elicited that he had apparently had pneumonia in 1949 associated with fever, chills, and cough.

Physical and clinical examination of the patient showed no abnormalities except for coarse rales which were heard over the posterior base of the right chest.

Roentgenographic studies of the chest were suggestive of a small mass or abscess at the right hilum. Bronchoscopy showed purulent secretions in the right lower lobe bronchus, and bacteriologic studies of the secretion cultured alpha streptococci and pneumococci. Bronchograms revealed no definite abnormality. A clinical diagnosis of lung abscess was made, and surgery was recommended.

A right thoracotomy was performed on July 27, 1950. A firm, round lesion could be palpated in the posterior and medial basilar segments of the right lower lobe, and this area of the lobe was sharply demarcated from the remainder of the lung by its light pink color, complete lack of anthracotic pigmentation, an apparently contracted state, and a definite fissure separating the involved segment from the rest of the lower lobe.

In the hilar dissection a pulsating, tortuous vessel, approximately 5 mm. in diameter, was encountered in the pulmonary ligament, which on dissection was found to run from the lower thoracic aorta to the posterior segment of the right lower lobe. The vessel had the appearance of a large intercostal artery. The abnormal vessel was ligated and divided, and the right lower lobectomy was completed.

Pathologic examinations showed a cystic mass 5 cm. in diameter which contained purulent material and was located in an area of lung which was pale, partially atelectatic, and

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FIG. 1 (Left). Thoracic postero-anterior roentgenogram in *Case 2*, showing round density along base of heart in right thorax.

FIG. 2 (Right). Lateral projection chest roentgenogram in *Case 2*, demonstrating round density in lower posterior right thorax.

contained no anthracotic pigment; no bronchial communication with the cyst could be demonstrated.

The patient's convalescence was complicated by partial atelectasis of the remaining right lung which necessitated one tracheobronchial toilet and one bronchoscopy before he fully expanded his lung. He was discharged on August 18, 1950, and has remained without symptoms.

*Case 2* (A. O. H.; No. 142 267). This 37-year-old white male was admitted to the hospital on October 21, 1952, with the complaints of small hemoptyses of eleven months' duration. A review of his past history revealed that he had been told he had a "cyst of the lung" from roentgenographic studies performed nineteen years previous to his admission.

Physical examination revealed a well-developed, well-nourished male in no acute distress. The blood pressure was 138 systolic and 88 diastolic in mm. of mercury; the pulse, 84; and respirations, 20 per minute. No unusual findings were noted except for scattered fine rales over the right lung field.

Roentgenographic studies of the chest showed a circumscribed mass in the medial basal segment of the right lower lobe (figures 1 and 2). A bronchoscopy performed on October 23, 1952, showed evidence of suppurative disease in the right lower lobe bronchi. Preoperative pulmonary function studies were within normal limits.

A right thoracotomy was performed on November 13, 1952. A mass approximately 7 cm. in diameter could be palpated in the posterior basal portion of the right lower lobe, and this area was clearly demarcated from the rest of the lung by a pale pink color and an incomplete fissure.

During mobilization of the lower lobe, three abnormal vessels were encountered entering the posterior segment of the lower lobe. After complete dissection it was found that the most cephalad of these vessels arose from the seventh right intercostal artery approximately 4 cm. lateral to the neck of the rib and was 5 mm. in diameter. Two additional vessels arose directly from the aorta below the seventh rib; one was 1 cm. and one was 5 mm. in diame-

FIG. 3. Photograph of resected right lower lobe (*Case 2*) after fixation and section to demonstrate the cyst in the posterior portion of the lobe with its surrounding vascular network.

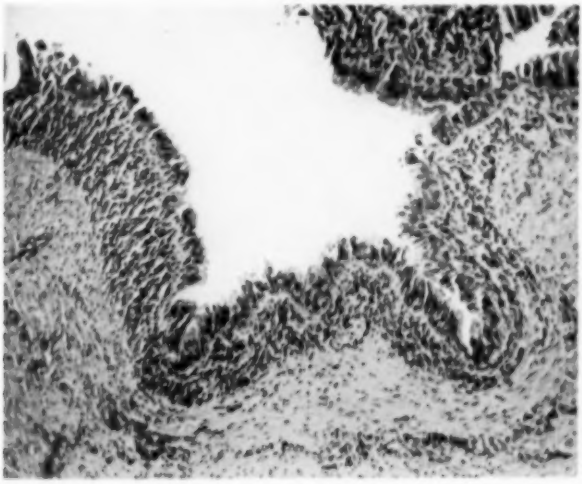

FIG. 4. Photomicrograph (×100) of cyst lining, *Case 2*, showing columnar, ciliated cells of respiratory epithelial type.

ter. All of these vessels entered the mass-bearing area of the lung. The vessels described were carefully ligated and divided after ascertaining that the normal hilar vessels were present.

A right lower lobectomy was performed, utilizing a hilar dissection technique. Pathologic examination revealed a large cyst containing a thick, brown, purulent fluid (figure 3). The cyst occupied a space in a small rim of lung tissue seemingly distinct from the rest of the lower lobe and appeared as described above. There was no demonstrable communication of the bronchial tree with the cyst. Microscopically, the cyst wall showed areas of columnar, respiratory epithelium, cartilage, and mucous glands (figure 4). In some areas the epithelium was completely denuded and replaced by an inflammatory exudate.

The patient's postoperative course was uneventful. He was discharged to his home on December 2, 1952.

*Case 3* (J. P.; No. 144-521). This 41-year-old white male was admitted to the hospital on March 20, 1953, with the complaints of progressive productive cough, hemoptysis, weakness, and dyspnea of seven years' duration. He had also noted intermittent, dull, right chest pain for one year. The past history and system review were noncontributory except for chronic alcoholism of ten years' duration.

Physical examination revealed a well-developed, well-nourished white male in no acute distress. The blood pressure was 132 systolic and 100 diastolic in mm. of mercury; the pulse, 80; and the respirations, 20 per minute. The only abnormalities noted were limited to the chest, where dullness to percussion and diminished breath sounds with post-tussive rales on auscultation were found. The patient was observed to be raising an average of 120 cc. of green-colored, foul sputum daily.

Clinical determinations showed the blood and urine to be normal. Six sputum examinations were negative for tubercle bacilli on microscopy and culture. Roentgenographic studies revealed an increased density at the right base and diminished excursions of the right hemidiaphragm. Bronchograms which were made prior to his hospital entry showed cystic spaces and saccular bronchiectasis of the right lower lobe basal segments. Bronchoscopy on March 10, 1953, revealed an inflammatory reaction in the right lower lobe bronchi. Pulmonary function studies demonstrated the patient's ventilatory reserve to be moderately below average.

A right thoracotomy was performed on April 7, 1953, using a posterolateral incision. The pleural space was entered through the right sixth intercostal space. The right lower lobe showed a marked contraction, and the basilar portion of the lobe presented a marked difference in external appearance from the remainder of the lung. There was an almost complete lack of crepitation in the basilar portion of the lobe, and in addition it was pale pink in color and was devoid of anthracotic pigment on its pleural surface in sharp contrast to the rest of the lung.

In the course of hilar dissection, a vessel 1 cm. in diameter was encountered which was found to course from the lower posterior basal area to the azygos vein where it entered on the medial aspect below the level of the fifth rib. The blood in the vein appeared oxygenated when the vessel was ligated and divided. A right lower lobectomy was completed.

On pathologic examination the lobe showed a large cyst covered by yellow-tan mucosa, and saccular bronchiectatic spaces were found in the remainder of the lobe. The basilar area of the lobe was not crepitant, and the external nonpigmented appearance was a sharp contrast to the darkly pigmented surface of the superior segment. Histologically, large cystic cavities lined by bronchial type of epithelium containing mucus and inflammatory cells were seen. Fibrosis and lymphocytes were seen in the surrounding lung parenchyma.

The patient's recovery was uneventful and he was discharged on May 1, 1953.

*Case 4* (J. J. LaM.; No. 148-792). A 35-year-old white carnival worker first entered the hospital on September 1, 1953, with the complaints of left chest pain, cough, and dyspnea of two days' duration. A review of his past history revealed that he had had seven episodes of pneumonia since the age of two years, the most recent one having been in 1942.

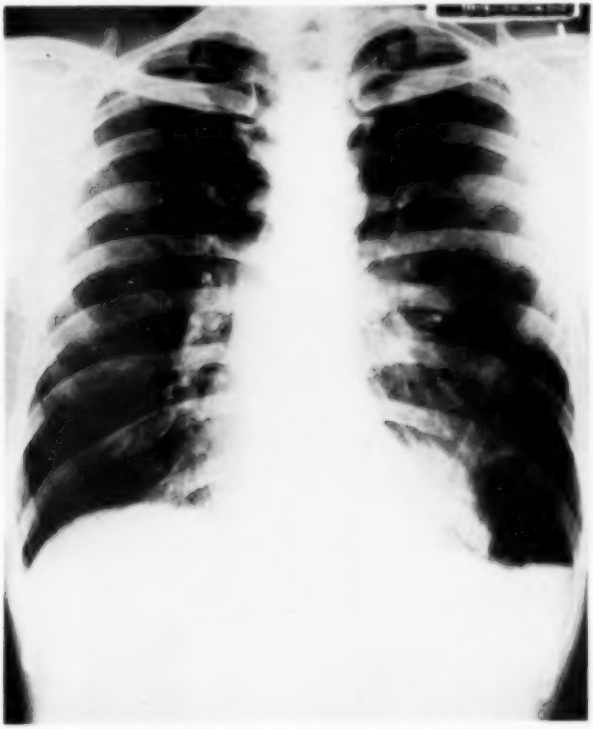

FIG. 5. Postero-anterior thoracic roentgenogram in *Case 4*, showing area of increased density in left lower chest along the left heart border thought to represent a basal atelectasis.

Physical examination was within normal limits except for coarse rales which were heard at the left base of the posterior chest. A bronchoscopy on September 24, 1953, showed no bronchial abnormalities. Roentgenographic studies demonstrated a posterior basal atelectasis (figure 5), and bronchograms showed no variations from normal except for the fact that the posterior basilar division was not well demonstrated. Because of the persistent basal atelectasis, surgery was recommended.

A left thoracotomy was performed on November 3, 1953, utilizing a posterolateral incision. The posterior basal area was clearly demarcated from the rest of the lung by its pink color and lack of anthracosis. In dissecting the inferior pulmonary ligament and incising the posterior mediastinal pleura, four large vessels were encountered which arose from the aorta and were traced to the posterior basal segment, which was distorted by a large firm mass (figure 6). These vessels varied in size from 1 cm. to 3 mm. in diameter, and they had the typical appearance and consistency of large systemic or peripheral arteries. A posterior basal segmentectomy was performed.

Pathologic examination of the specimen revealed a multiloculated cyst with a gray, mucosal lining (figure 7). On microscopic examination, the cyst wall contained cartilage, muscle, fibrous tissue, lymphocytes, mucous glands, and was lined by a tall, columnar, ciliated epithelium. The abnormal vessels had the histologic appearance of arteries, although the media in some was slightly smaller than might be expected in a peripheral artery of com-

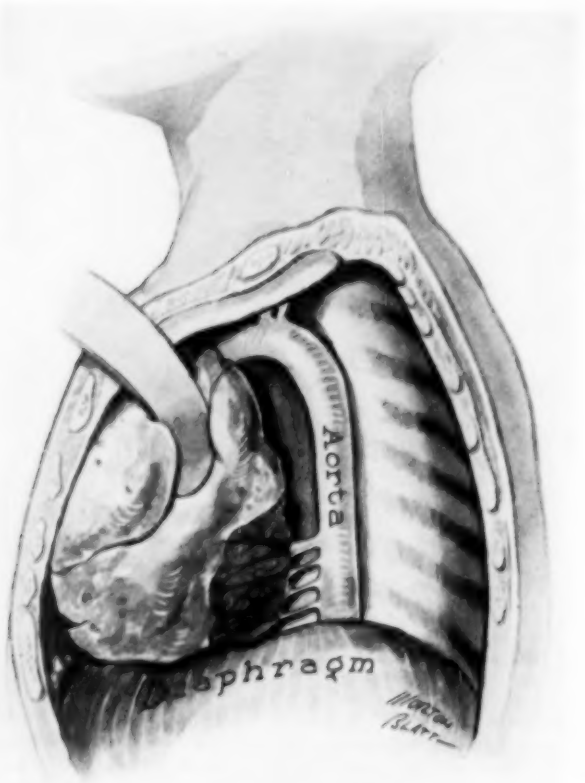


FIG. 6. Artist's diagrammatic representation of the four anomalous aortic branches which were found to enter the posterior portion of the left lower lobe at surgery.

parable size. There were no demonstrable bronchial communications with the cyst nor could definite sites of communication of the abnormal vessels with the pulmonary circulation be established, except by inference, because the bronchial and segmental veins were considerably larger than normal.

The patient was discharged with his wound healed, lung fully expanded, and asymptomatic on November 18, 1953.

*Case 5* (G. A. J.; No. 151-372). A 39-year-old white male truck driver was admitted to the hospital on December 18, 1953, with the chief complaint of dull, aching right chest pain of eleven years' duration. His history revealed that a lesion of the lower right lobe had been discovered while he was in the military service in 1942. The patient also complained of exertional dyspnea and frequent upper respiratory infections.

The physical examination showed no abnormalities. Clinical studies of the blood and urine were within normal limits. Roentgenograms of the chest disclosed a rounded density 5 cm. in diameter in the medial basilar area (figure 8). Pulmonary function studies were normal. A preoperative diagnosis of intrapulmonary bronchogenic cyst was made.

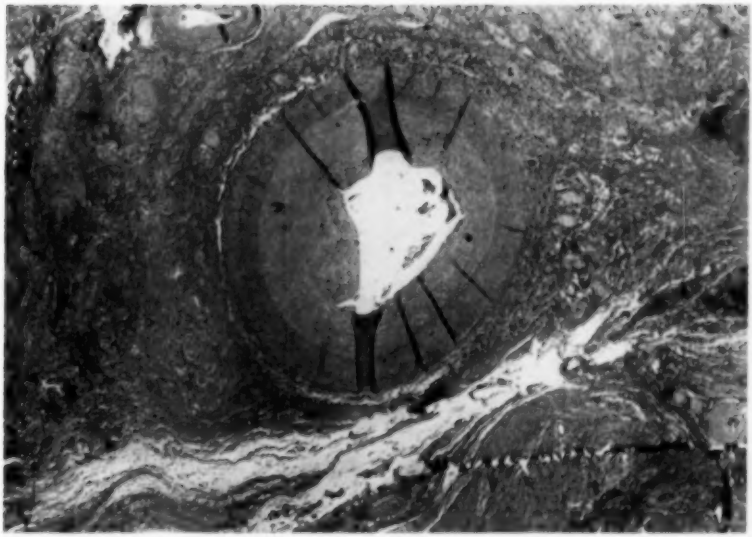

FIG. 7. Cross section (×40) of anomalous aortic branch, from *Case 4*, showing histologic features of arterial wall.

FIG. 8. Chest roentgenogram (postero-anterior) in *Case 5* which revealed round density at right cardiophrenic angle.

FIG. 9 (Left). Photograph taken at surgery showing inferior pulmonary ligament and subpleural bulge of anomalous artery.

FIG. 10 (Right). Surgical photograph made after dissection of the inferior pulmonary ligament to show the anomalous aortic branch to the sequestrated part of the right lower lung.

A right thoracotomy was performed on January 14, 1954, through a posterolateral incision. The pleural space was entered through the right sixth intercostal space, and the lung was mobilized by sharp dissection. A firm mass 5 cm. in diameter occupied the area of posterior and medial basilar segments, and this area appeared distinct from the remaining portion of the lung because of lack of crepitation, a pale nonpigmented color, and an incomplete fissure.

During the dissection of the right lower lobe, a large artery, 1 cm. in diameter, was found in the inferior pulmonary ligament which originated from the aorta just above the aortic hiatus and entered the diaphragmatic surface of the lesion-containing area of the lung (figures 9 and 10). After all of the hilar vessels were exposed and found to be normal, the abnormal artery was ligated and divided. A right lower lobectomy was then performed.

This lesion on examination proved to be a multilocular cyst filled with a green-brown viscid material. On microscopic examination, the cyst was lined by a pseudostratified columnar and flattened cuboidal epithelium. The wall of the cyst contained cartilage, fibrous tissue, and inflammatory cells. The surrounding lung parenchyma gave evidence of diffuse inflammatory changes.

The patient's postoperative course was uneventful, and he was discharged without abnormal findings or symptoms on January 29, 1954.

## DISCUSSION

It is interesting that the first surgical report of an abnormal pulmonary vessel associated with intrapulmonary cystic disease (13) should have emphasized so vividly the

surgical importance of this lesion. Indeed, the patient reported in that communication succumbed as the result of hemorrhage from inadvertent transection of the vessel. Since that paper, additional fatalities have been reported as the result of similar accidents at surgery, and a number of writers (3, 14–17) have described serious technical difficulties arising from injury to the anomalous vessels. The 5 cases included in this paper re-emphasize the potential hazards of the vascular anomalies.

All of the patients in the present series were males between the ages of twenty-five and forty-one years. The lower lobe was involved in each, but, in contrast to other series reported, the abnormalities appeared in the right lung in a ratio of four to one. In 4 cases there was no bronchial communication with the cyst, and in all of these a definite systemic arterial anomaly existed. In one patient a definite bronchial connection was present, and the cyst was associated with bronchiectasis. The vascular abnormality in this case was venous in character, but, because of the clinical course and surgical findings, it deserves inclusion in this same group of pathologic lesions. In 2 patients the vascular abnormality presented multiple arterial divisions, all arising from the aorta except one branch in *Case 2* which arose from an intercostal artery.

There was no clear-cut clinical syndrome which distinguished these intrapulmonary bronchial cysts from other chronic pulmonary diseases. In the cases herein reported the prominent feature was the chronic and recurring nature of the symptoms, such as cough, expectoration, hemoptysis, and dyspnea. This was a similar experience to those encountered by previous writers (1, 4, 18, 19). The roentgenographic picture also was variable in that the findings were those of possible abscess (*Case 1*); a segmental atelectasis suggestive of carcinoma (*Case 4*); a round lesion (*Case 5*); and a definite cystic-appearing lesion (*Case 2*). It is evident then that a suspicion of these sequestrated lesions must be engendered when patients are seen with histories of chronic pulmonary disease, cystic lesions, or with ill-defined roentgenographic findings. More detailed roentgenographic features have been stressed by Wyman and Eyler (20), as noted in their large series of cases.

One gross characteristic noted at surgery was common to all 5 of the cases reported, and that was the difference in appearance of the sequestrated or lesion-bearing portion of the lung. In all of these specimens the cystic area showed an absence of anthracotic pigmentation, and the lung appeared pale pink like the lung of an infant. Findings of this type may be seen in other pulmonary lesions but, as the result of the present experience, it is believed that when found they should cause the operator to search carefully for anomalous vessels if he is planning to perform any resection. As mentioned above, the cysts in all 5 patients occurred in the lower lobes, and all but 2 of the abnormal vessels were found below the hilum in the inferior pulmonary ligament. The fact that cysts and anomalous vessels may occur elsewhere in the chest and even in the abdomen, however, has been documented (9, 17, 21, 22).

Pathologically, the pulmonary lesions have been characterized by cystic structures usually lined by columnar or ciliated epithelium, with cartilage and mucous glands in the wall and varying degrees of inflammation in the surrounding parenchyma. It has been the writers' impression that the anomalous arterial branches have been typical grossly and histologically of peripheral arteries. One unusual characteristic, however, was the presence of arteriosclerotic changes in most of these arterial divisions.

There have been two principal schools of thought on the embryologic origin of these lesions. One of the earliest formulations was that of the isolated diverticular theory of origin from the primitive foregut (6, 22–24), with the vascular anomalies considered to be

a secondary factor. The possibility, however, of the vascular abnormality causing the pulmonary-bronchial dissociation and consequent anomaly has more recently received considerable attention (1, 3, 8, 13, 18).

SUMMARY

Five cases of intrapulmonary cystic lesions and anomalous hilar vessels have been presented to emphasize the surgical hazards created by the vascular abnormalities.

The variability of clinical history and roentgenographic findings makes preoperative diagnosis difficult. Nevertheless, the presence of chronic, nonspecific pulmonary disease and roentgenographic findings suggestive of a cyst or localized disease in the lower lobe should alert the physician to the possibilities of this lesion.

The discovery at thoracotomy of a pulmonary lesion in an area demarcated by difference in color, lack of anthracotic pigmentation, and/or loss of crepitation should warn the operator to exercise care in the hilar dissection and to search for anomalous vessels.

SUMARIO

*Anomalías Vasculares Asociadas con Quistes Bronquiales Intrapulmonares*

Preséntanse 5 casos de lesiones quísticas intrapulmonares y vasos hiliares anómalos para recalcar los riesgos quirúrgicos creados por las anomalías vasculares.

La variabilidad de la historia clínica y de los hallazgos radiográficos hace difícil el diagnóstico preoperatorio, pero los enfermos que manifiestan afección pulmonar anespecífica crónica y hallazgos radiográficos indicativos de quiste o de enfermedad localizada en el lóbulo inferior deben poner sobre aviso al médico en cuanto a la posibilidad de dicha lesión.

El descubrimiento, en la toracotomía, de una lesión pulmonar en una zona demarcada por el distinto color, falta de pigmentación antracótica y/o pérdida de crepitación debe excitar al operador a desplegar cautela en la disección hiliar y a buscar vasos anómalos.

RESUME

*Anomalies vasculaires associées aux kystes bronchiques intrapulmonaires*

Cinq cas de lésions kystiques intrapulmonaires avec anomalies des vaisseaux hilaires sont présentés, pour bien montrer les risques opératoires créés par ces anomalies vasculaires.

La variabilité de l'histoire clinique et des constatations radiologiques rendent le diagnostic pré-opératoire difficile, mais chez les patients qui présentent une affection pulmonaire chronique non spécifique et des images radiologiques suggérant le diagnostic de kyste ou d'affection localisée au niveau du lobe inférieur l'attention du médecin doit être attirée sur la possibilité des telles lésions. La découverte d'une zone délimitée par une différence de coloration, l'absence de pigmentation anthracosique et la perte de crépitation, ou ces deux phénomènes, à l'occasion d'une thoracotomie pour lésion pulmonaire, doit avertir l'opérateur de la nécessité d'être prudent dans la dissection hilaire et de rechercher l'anomalie vasculaire.

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# COMBINED PNEUMOCOCCAL AND TUBERCULOUS MENINGITIS[1]

## Report of a Case

EDGAR ALSOP RILEY[2]

(Received for publication August 27, 1954)

Cases of spontaneously occurring meningitis produced by *Mycobacterium tuberculosis* and another microbial species are unusual. In 1948 (1) the writer reported a case of mixed tuberculous and meningococcal meningitis, and at that time found in the literature reports of thirty-three similar cases. Recently a similar case of combined pneumococcal and tuberculous meningitis came to the writer's attention. It was believed that the case was sufficiently interesting to report in its own right and at the same time an opportunity was provided to review any additional cases which might have appeared in the literature since 1948.

### CASE REPORT

The patient was a 45-year-old white man, M. F., who was admitted to Bellevue Hospital with a chief complaint of weakness and pain in the right posterior chest for two weeks. Except for a mild chronic cough with small amounts of morning sputum, the patient was well until December 24, 1947, approximately two and one-half weeks before admission, when he noted the rather insidious onset of a "cold" characterized by coryza, frontal headache, mild feverishness with chilly sensations, and marked weakness. His appetite was poor, and during his illness he had lost a definite but unknown amount of weight. He remained at home in bed during the holidays, but returned to work two days later. At this time he developed a cough productive of approximately one-half cup of watery nonfoul, nonbloody sputum each day, and noted the onset of an intermittent, dull, nonpleuritic, nonradiating pain in the right posterior chest. Because of severe weakness approaching prostration, he was forced to stop work, remaining in bed at home. Headache became more marked, and the patient remembered little of events during the few days immediately prior to admission. He denied similar past illnesses, hemoptysis, hoarseness, night sweats, pleuritic pain, or true chills. He had been mildly short of breath on exertion during his illness, without edema or orthopnea. System review was negative.

On admission to the hospital the patient was a thin, small asthenic middle-aged white male who was chronically and acutely ill. His temperature was 101.6°F.; pulse, 132; respirations, 40 per minute; and blood pressure, 210 systolic and 130 diastolic in mm. of mercury. There was marked dyspnea, but no orthopnea. An occasional moist cough was productive of small amounts of brownish sputum. There was herpes of the right upper lip. The mucous membranes of the mouth were dry, the pharynx injected, and the tongue was beefy. The teeth were in poor condition. The larynx was not visualized. There was mild resistance on passive flexion of the neck. The trachea was in the midline. The neck veins were not distended. There was no local or generalized lymphadenopathy. The thorax was symmetrical, with a minimal lag on the right. Examination of the lungs revealed dullness with increased tactile fremitus on the right from the apex to the fourth rib anteriorly. In this area bronchial breath sounds with pectoriloquy were noted, but no rales or rhonchi. Dullness was noted at the right apex posteriorly. The left chest was clear. The heart was not clinically enlarged. A regular sinus rhythm with sinus tachycardia was present. No murmurs were heard. The abdomen was moderately distended. Both epididymi were slightly enlarged and firm. The prostate was symmetrically enlarged. There was no cyanosis, club-

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bing, or edema. The radial arteries were moderately thickened. The cranial nerves were intact. Superficial and deep reflexes were present and equal. The Babinski response was plantar. There was no Kernig sign, but an equivocal Brudzinski sign was noted. The patient was rational.

The initial laboratory examination revealed a hemoglobin of 16 gm., a leukocyte count of 20,700 leukocytes per cu. mm., with a differential count of 96 per cent polymorphonuclear cells and 4 per cent lymphocytes. The admission urinalysis showed a specific gravity of 1.015, 2-plus albuminuria, and 2 to 6 leukocytes per high-power field, with occasional clumps. A casual sputum smear was negative for acid-fast bacilli. A sputum Gram stain showed small, lancet-shaped, encapsulated Gram-positive diplococci. Both blood and sputum cultures grew type XII pneumococci. A chest roentgenogram showed a pneumonic infiltration confined to the upper and middle lobes of the right lung (figure 1).

Following establishment of a diagnosis of a pneumococcal pneumonia, the patient was placed in an oxygen tent, given infusions with vitamins, and was started on a regimen of penicillin, 50,000 units every three hours intramuscularly. On the third hospital day, because of continued frontal headaches, drowsiness, and slight pain on flexion of the neck with a suggestive Brudzinski sign, lumbar puncture was performed. The fluid obtained was cloudy, contained 6,450 leukocytes per cu. mm., all of which were polymorphonuclear leukocytes. Small Gram-positive cocci were demonstrated on smear, but culture showed no growth. The penicillin concentration of the cerebrospinal fluid withdrawn was 0.20 $\gamma$ per ml. The cerebrospinal fluid glucose content was 0 mg. per 100 ml.

During the patient's hospitalization, twenty-two lumbar punctures were performed. By the fifteenth hospital day, the number of leukocytes had fallen to 97 per cu. mm., with 41 per cent polymorphonuclear leukocytes and 56 per cent lymphocytes, and the cerebrospinal fluid sugar had risen to 38 mg. per 100 ml. The protein content remained elevated at 135 mg. per 100 ml. On subsequent lumbar punctures, the leukocyte count varied from 42 to 600 cells per cu. mm., with a preponderance of lymphocytes on most determinations. The protein determination ranged between 45 and 154 mg. per 100 ml., and the glucose values were usually below 50 mg. per 100 ml. The fluid, initially turbid, became clear on the fif-

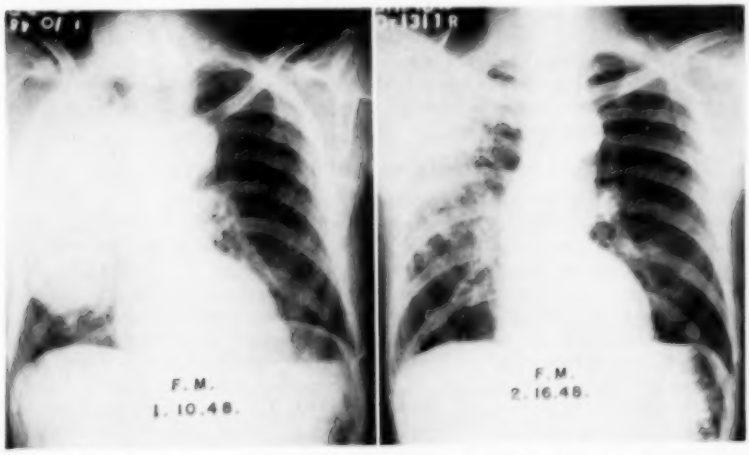


FIG. 1 (Left). Chest roentgenogram taken on January 10, 1948, showing pneumonic consolidation of the right upper and middle lobes.

FIG. 2 (Right). Chest roentgenogram taken on February 16, 1948, showing considerable resolution of the right upper and middle lobe pneumonia.

teenth hospital day and remained so until approximately two weeks before death, when it became turbid once again and remained so until the patient's death.

Following the initial findings, the patient received 100,000 units of penicillin intrathecally, and on each of the six subsequent days received 100,000 units of intrathecal penicillin in addition to intramuscular penicillin. From initial irregular rises to 103.4° F., the patient's temperature gradually returned to normal by the fifth day of therapy, where it remained until the latter part of his illness. At the end of the first ten days of therapy, symptomatic and objective improvement was marked and penicillin was discontinued. The patient continued to complain of inconstant headache and a severe herpetiform eruption involving not only the lips but tongue and buccal mucous membranes, which subsided gradually over the next two weeks. The physical signs in his lungs gradually cleared, cough improved, and sputum diminished (figure 2). Following the initial specimen, subsequent blood and sputum cultures were negative for pneumococci.

Although showing progressive clinical improvement, on the thirteenth and fifteenth hospital days, isolated acid-fast bacilli on direct smear on each of two cerebrospinal fluid specimens were found. In view of the patient's clinical improvement, this finding proved difficult to interpret, particularly in view of the fact that all succeeding cerebrospinal fluid specimens were negative for acid-fast bacilli until on the forty-first day of illness, when a smear was again reported positive. On the thirteenth and nineteenth hospital days, acid-fast bacilli were noted on direct smear of the patient's sputum. Culture of the specimens of cerebrospinal fluid which were positive on direct smear for acid-fast bacilli were consistently negative for tubercle bacilli. In spite of these bacteriologic findings, which were considered to represent laboratory errors, no specific antituberculous chemotherapy was instituted.

The patient's clinical improvement continued and he remained afebrile until approximately his fiftieth hospital day, when it was noted that a marked but gradual change in his mental state was occurring. Although he was mentally clear, well oriented, and showed facility in calculation and other tests, he became less neat about his person, showed sloppiness in handling his food, and became less alert and somewhat drowsy. His temperature began to rise, and on the fifty-seventh hospital day he developed neurologic findings consisting of a left central type of facial weakness, ptosis of the left lid, complete paralysis of the left internal rectus muscle, slight deviation of the tongue to the left, a slightly stiff neck with a questionably positive Brudzinski sign, slight spooning of the left hand, and an increase of the knee jerks on the left. The remainder of the physical and neurologic examination was within normal limits. The patient's drowsiness increased until, by the sixty-second hospital day, he could no longer be aroused. Cheyne-Stokes respiration developed, and he died quietly on his sixty-seventh hospital day.

### *Post-Mortem Examination*

Only the pertinent gross and microscopic findings will be reported.

*Gross examination:* On post-mortem examination, the body was that of an emaciated 45-year-old white male with moderate rigor mortis. The skin appeared normal, with numerous small needle punctures over the fourth lumbar interspace. The pupils were dilated, equal, and regular. Upon opening the body through a Y-shaped incision, the peritoneum was found to be smooth and glistening. The liver was smooth and enlarged to 4 cm. below the costal margin. The spleen was small and firm. No free fluid was present in either pleural cavity. There were fibrous adhesions between the upper right lung and chest wall and also between the pericardium and epicardium. The pericardial cavity was slightly roughened, with a few adherent strands of fine fibrous material. The epicardium was also slightly roughened. There were a few soft deeply pigmented noncalcified mediastinal nodes measuring 1 to 2 cm. in length.

Examination of the heart was normal except for a small vegetation which measured approximately 1 by 4 cm. on one of the cusps of the tricuspid valve and a similar vegetation on the anterior cusp of the mitral valve. The ascending and descending portions of the aorta showed moderate atheromatous and calcific deposits.

Examination of the lungs revealed the visceral pleura of the right upper lobe adherent to the parietal pleura and moderately thickened. The trachea and bronchi were normal throughout, containing a small amount of thin, yellow mucopurulent discharge. The right upper lobe was contracted and nodular and, on section, was studded with small firm yellow nodules measuring up to 1 cm. in diameter. There were several small multiloculated cavities, some containing light yellow cheesy material, the largest of which measured 2 cm. in diameter. The remainder of the right lung was normal, and no abnormalities were noted in the left lung.

A small white tubercle measuring approximately 1 mm. in diameter was found on the anterior surface of the right lobe of the liver. A similar tubercle was present on the anterior surface of the left kidney. A depressed white scar measuring 1 by 1 cm. was on the anterior upper surface of the right kidney.

Examination of the brain revealed a normal dura with numerous patches of tough yellowish organized exudate beneath the meninges at the base of the brain and over the cerebral hemispheres. Numerous small white tubercles measuring 0.5 to 1 mm. were at the base of the brain.

*Microscopic examination:* The myocardial muscle fibers were replaced with fibrous tissue in a few small areas. The epicardium was slightly thickened. There was an occasional area of lymphocytic reaction just beneath the pericardium. There was a small area of organizing exudate on the tricuspid and mitral valves and a small calcific deposit was in the tricuspid ring. Examination of the aorta revealed a thickened intima with hyalinization, calcification, cholesterol clefts, lipoid deposits, and small areas of necrosis with ulceration of the endothelium.

Sections from the upper lobe of the right lung revealed a thickened pleura with fibrous tissue tags attached to the surface. The parenchyma contained numerous areas of caseous necrosis with mononuclear cell infiltration, tubercle formation, and multinucleated giant cells. The bronchioles contained debris and many lymphocytes and polymorphonuclear cells. The alveolar spaces contained pigment-laden phagocytes, lymphocytes, plasma cells, and polymorphonuclears. Sections taken from the right lower lobe showed alveolar vessels congested with erythrocytes. There were patchy areas of lobular bronchopneumonia.

Sections of kidney revealed a portion of the cortex containing organizing granulation tissue, with perivascular collections of lymphocytes, monocytes, and plasma cells. The glomeruli in this region were replaced with fibrous tissue.

A mediastinal lymph node contained an occasional tubercle and multinucleated giant cell. There was one small focal area of necrotic cells in the pituitary.

### *Brain and Meninges*[3]

*Gross description after fixation:* "The vessels at the base show a slight sclerosis. There is a grayish exudate in the interpeduncular space and also a slight but definite exudate over the cerebral hemispheres, particularly along the upper part of the median surface. There is marked congestion of the pial veins and capillaries. The ventricles are approximately normal in size. There are a few patches of exudate seen in the cerebral hemisphere which are slightly larger in size than the usual tubercles seen in tuberculous meningitis. No conglomerate tubercles are noted on careful section of the brain."

*Microscopic report:* "Section of meninges at the base of the brain shows a thick cellular exudate which is largely mononuclear, although some polymorphonuclear cells are present. There are several small granulomatous masses in their leptomeninges containing a few giant cells. There is a definite cellular infiltration of some of the veins and arteries."

### *Final Pathologic Diagnosis*

Fibrocaseous tuberculosis of lung with cavitation, right upper lobe
Tuberculosis of mediastinal lymph nodes, liver, kidney, and meninges

[3] Examination made by Dr. L. D. Stevenson.

Resolved lobar pneumonia (pneumococcus type XII—clinical)
Resolved pneumococcal meningitis (clinical)
Healed acute bacterial endocarditis (tricuspid and mitral valves)
Fibrous pleural adhesions, right
Focal fibrosis of pericardium
Focal myocardial fibrosis
Atherosclerosis of aorta
Calcification of tricuspid ring
Arteriosclerotic scars of kidneys

## DISCUSSION

The diagnosis of tuberculous meningitis in this case was based upon the presence of the characteristic histopathologic findings of tuberculous infection in lungs and central nervous system in addition to the findings of acid-fast bacilli in the cerebrospinal fluid. Culture of the cerebrospinal fluid revealed no tubercle bacilli and, unfortunately, no acid-fast stains were done on the tissue examined.

Since the introduction of intrathecal medication in the treatment of tuberculous meningitis, cases of superimposed nontuberculous bacterial meningitis secondary to intrathecal therapy have been occasionally reported. A case of tuberculous meningitis complicated by a superimposed *Streptococcus faecalis* meningitis was reported in 1950 by Rosenthal and co-workers (2). Two similar cases of superimposed infection were reported by Calamari (3), and there are undoubtedly other cases which have not appeared in the medical literature.

As previously noted, cases of spontaneously occurring mixed tuberculous and nontuberculous meningitis are rare. A review of approximately ninety cases of tuberculous meningitis seen at the New York Hospital between 1932 and 1954 failed to reveal any cases of mixed infection. Moreover, the present case is the only example of a mixed nontuberculous and tuberculous meningitis which has been observed among approximately 385 cases of tuberculous meningitis on the Bellevue Hospital Chest Service between 1920 and 1954.

Since 1947, a few additional cases of spontaneously occurring mixed nontuberculous and tuberculous meningitis have been reported (table 1). An extraordinarily large series of cases was reported in 1952 from Florence by Giusti and Barilli (12), but has purposely been excluded from this group of cases for reasons which deserve some discussion. These writers report sixty cases of purulent meningitis, in thirty of which the etiologic agent was unidentified, which were superimposed upon tuberculous meningitis during therapy. It is difficult to understand why so many cases should be reported from one clinic, more than the total number of cases appearing from all other sources. In reviewing this article one is forced to the conclusion that the majority of these superimposed pyogenic infections were iatrogenic in origin, secondary to either intrathecal medication or to intraventricular catheterization. The sixty cases occurred over a four-year period in a series of 512 cases of tuberculous meningitis, an amazingly high incidence of approximately 12 per cent. The secondary infections developed most frequently in the hot summer months, were most numerous among those patients in whom intraventricular catheterization had been performed, and usually occurred only four to five months after the antituberculous chemotherapy had been initiated.

With the exception of these sixty cases, therefore, approximately forty-seven cases of mixed nontuberculous and tuberculous meningitis have been reported. The case of the present report increases the total number to forty-eight, exclusive of the Giusti and Barilli cases.

TABLE 1

CASES OF SPONTANEOUSLY OCCURRING MIXED NONTUBERCULOUS AND TUBERCULOUS MENINGITIS REPORTED IN THE LITERATURE

| Number of Cases | Bacteriology | Author |
|---|---|---|
| 34 | (Previously collected) | Riley (1) |
| 1 | Tubercle bacillus and meningococcus | Lejmbach (4) |
| 1 | Tubercle bacillus and pneumococcus | Camisasca (5) |
| 6 | Tubercle bacillus and meningococcus | Choremis *et al.* (6) |
| 1 | Tubercle bacillus and *H. influenzae* | Cucullo and Rovarella (7) |
| 1 | Tubercle bacillus and staphylococcus | Swisher (8) |
| 1 | Tubercle bacillus and pneumococcus | van den Bosch (9) |
| 1 | Tubercle bacillus and meningococcus | Petit and De Ripainsel (10) |
| 1 | Tubercle bacillus, alpha hemolytic streptococcus and meningococcus | Williams and Clapp (11) |
| 60 | Not specified in all cases | Giusti and Barilli (12)* |
| Total: 107 | | |

* See text for explanation why these cases are not included in the final compilation.

From a review of the forty-seven reported cases, three chronologic patterns emerge. In a few cases the nontuberculous and the tuberculous meningitis are diagnosed at the same time and the diagnosis of a simultaneous mixed infection can be made unequivocally. It is more usual, however, for the nontuberculous infection to precede the tuberculous one, or vice versa, so that, clinically, one is superimposed upon the other. This was true in the case under discussion, although there would seem to be little doubt but that the tuberculous meningitis was probably well established pathologically when the clinical diagnosis of pneumococcal meningitis was made. Only eight days elapsed between the recovery of Gram-positive cocci from the cerebrospinal fluid and the appearance of acid-fast bacilli. In other instances, such as the cases reported by Choremis and associates (6), the pyogenic infection may complicate an established case of tuberculous meningitis and can be regarded as a secondary rather than simultaneous mixed infection.

The relationship between the two types of meningitis, either occurring in succession or simultaneously, is not clear. The situation may be a purely fortuitous one. It has been suggested (11), however, that the meninges are infected first by only one species of microorganism and that the resultant inflammation renders the meninges more susceptible to invasion by any circulating bacteria. When the nontuberculous bacterial infection precedes the tuberculous one, it has been postulated (1) that perhaps the suppurative process has reactivated a latent subarachnoid partially encapsulated tuberculous lesion with liberation of tubercle bacilli into the subarachnoid space and the development of an active tuberculous meningitis. Without specifically incriminating intrathecal treatment, Choremis and associates (6) state they never saw a nontuberculous bacterial infection superimposed upon tuberculous meningitis prior to the era of streptomycin therapy. In a discussion of their sixty cases, Giusti and Barilli (12) postulate several possibilities in addition to secondary infection occurring as a result of treatment. As the majority of their cases developed during the hot summer months, they believed that climatologic conditions played a predisposing role, the exact nature of which is not clear. They also believed that some of their cases resulted from a superimposed influenzal epidemic which occurred on their wards, predisposing to secondary bacterial infection.

Recognition of a mixed or secondary infection is important from the standpoint of the proper choice of antimicrobial drugs. The patient whose case is the subject of the present report received no specific antituberculous chemotherapy because, in view of the presenting clinical picture, the finding of tubercle bacilli in both sputum and cerebrospinal fluid was believed to represent a laboratory error. An unexpected change in the cerebrospinal fluid should arouse suspicions to the possibility of a mixed or superimposed infection, regardless of whether the nontuberculous or the tuberculous infection is the initiating one. It is perhaps superfluous to add that the cerebrospinal fluid from all cases of meningitis should be cultured for bacteria other than tubercle bacilli before therapy is begun because the characteristic cerebrospinal fluid findings of either form of meningitis might be masked by the duality of the infection. Of the forty-eight cases reported of mixed superimposed tuberculous and nontuberculous meningitis in the literature, thirty-one were due to the combination of the tubercle bacillus and meningococcus, seven to the combination of the tubercle bacillus and pneumococcus, four to a combination of the tubercle bacillus and some unknown organism, two to a combination of the tubercle bacillus with Friedländer's bacillus, one each to a combination of the tubercle bacillus with *Micrococcus tetragenus*, *Staphylococcus*, *Hemophilus influenzae*, and one to a triple infection with the tubercle bacillus, *Streptococcus hemolyticus*, and meningococcus.

SUMMARY

A case of spontaneously occurring mixed tuberculous and pneumococcal meningitis is reported and the pertinent literature is reviewed.

SUMARIO

*Meningitis Tuberculosa Neumocócica Combinada: Presentación de un Caso*

Se presenta un caso de meningitis tuberculosa y neumocócica mixta que ocurrió espontáneamente y se repasa la literatura.

RESUME

*Méningite tuberculeuse et pneumococcique mixte: Rapport d'un cas*

Un cas de méningite tuberculeuse et pneumococcique mixte apparu spontanément es rapporté; la littérature pertinente est commentée.

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(8) Swisher, S. N.: Meningitis due to simultaneous infection with *Mycobacterium tuberculosis* and *Staphylococcus*, Minnesota Med., 1952, *35*, 420.
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(10) Petit, R., and De Ripainsel, M.: A propos d'un cas de méningite double, meningococcique et tuberculeuse, Acta paediat. belg., 1952, *6*, 139.
(11) Williams, M. J., and Clapp, M. P.: Mixed meningitis, J.A.M.A., 1953, *151*, 732.
(12) Giusti, M., and Barilli, L.: Studio casistico e clinico su 60 casi di meningite sourammessa a meningite tubercolave in corso di trattamento, Riv. clin. Pediat., 1952, *50*, 529.

# *Editorial*

## Problems of Immunity in Nontuberculous Infections[1]

Recent investigations have considered the role of host defense and the relationship of antimicrobial treatment in rickettsial infections and certain diseases caused by Gram-negative bacteria.[2, 3] The concern has been whether antimicrobial therapy, although helpful in controlling the acute manifestations of illness, has interfered in any way with the natural development of the immune state. It may be concluded that the very early treatment of the acute infection does alter in some way the degree of immunity.

The rickettsial infections and typhoid fever provide information with regard to host immunity and the time and duration of antimicrobial treatment.

The rickettsial infections, typhoid fever, tularemia, and brucellosis all have the common factor of intracellular habitat of the offending microbe and a tendency for each illness to relapse during periods varying from days to months to years.

The initial observations with chloramphenicol in scrub typhus[4] demonstrated that the acute manifestations of the disease, including the fever, abated within approximately one day after the commencement of therapy. It was initially surmised that antimicrobial treatment should be continued until approximately the twelfth day of disease, when antibodies were ordinarily known to appear. This continued course was unnecessary, as it was soon demonstrated that patients first treated on the sixth day of illness or later responded rapidly and did not relapse in spite of the fact that the drug was given for only twenty-four hours.

The investigations of the Army group in Malaya then shifted to antimicrobial prophylaxis of disease and studies of immunity.[5] Human volunteers were exposed to scrub typhus in areas known to be highly infested with typhus-bearing mites. These studies, conducted with groups receiving antimicrobials on one hand and with appropriate control groups on the other, resulted in infection rates sufficiently high to permit valid conclusions. Under these conditions, patients with the disease became available for study very early in the course of infection. In patients treated prior to the fifth febrile day, the initial therapeutic response to chloramphenicol was prompt; yet, approximately eight days after the drug was discontinued, a full-blown relapse ensued with rickettsemia again demon-

[1] This editorial was based in part on a paper presented at the Thirteenth Veterans Administration, Army, Navy Conference on the Chemotherapy of Tuberculosis, held at St. Louis, Missouri, February 8–11, 1954.

[2] Smadel, J. E.: Influence of antibiotics on immunological responses in scrub typhus, Ricketts Award Lecture, University of Chicago, May, 1953.

[3] Woodward, T. E. *et al.*: M. Clin. North America, 1954, p. 577.

[4] Smadel, J. E., *et al.*: J. Clin. Investigation, 1949, *28*, 1196.

[5] Smadel, J. E. *et al.*: Am. J. Hyg., 1949, *50*, 75.

strated. The possibility was immediately raised that relapse might have been prevented by prolonging the initial course of treatment. This point was duly considered.

Other members of this volunteer series received a short, twenty-four-hour course of choramphenicol on or before the fifth day of disease. After the defervescence and prior to recrudescence, the drug treatment was repeated usually when rickettsemia was demonstrable. In these subjects, the intermittent spacing of the antimicrobial permitted sufficient immunity to develop without relapse.

It seemed apparent at this stage of the investigations that sufficient immunity to arrest the course of infection usually resulted from the antigenic stimulus during approximately a week of the natural disease. Expressed another way, when specific therapy began on or after the sixth day of disease, relapse in scrub typhus did not occur, regardless of the duration of treatment. On the other hand, when treatment was given quite early, prior to the fifth febrile day, relapse ensued approximately eight days after treatment was discontinued. Other human trials were conducted in which rickettsiostasis was maintained by daily antimicrobial treatment for twenty-eight days after an artificially induced infection. Suppressive antibiosis for twenty-eight days was insufficient time for immunity to develop; and full-blown, active disease occurred in this group on cessation of drug administration.

One of the crucial trials in naturally infected human volunteers provided for the intermittent administration of chloramphenicol at seven-day intervals, a schedule designed to permit the host to develop his own defense. Continuation of these intermittent courses up to the thirty-fifth day prevented the disease from appearing in the active sense. However, mild headache and low-grade fever noted just prior to several of the intermittent doses were undoubtedly manifestations of infection. At these times, *Rickettsia orientalis* were readily isolated from the patient's blood. By further adjusting the dose of chloramphenicol and treatment interval (four-day intervals up to the twenty-fifth day), it was possible to completely suppress the clinical disease. Moreover, rickettsemia was demonstrated, and immunity subsequently developed. Immunity, therefore, comes at a price, dependent in large part upon the mass of antigenic stimulation and resultant immune response.

It should be mentioned that viable rickettsiae have been isolated from tissues of well persons several years after active infections of scrub typhus and Rocky Mountain spotted fever.[6, 7] Furthermore, in the rickettsiosis of the Brill's type, latent rickettsiae may re-emerge to cause active disease twenty years or more after the initial typhus infection.

Some of these concepts apply in typhoid fever, one of the important Gram-negative diseases. Suppressive antimicrobial therapy with chloramphenicol has been continued in some patients up to the sixtieth day of disease. Nevertheless, even under these conditions, relapses, with bacteremia, ensued approximately

[6] Smadel, J. E., *et al.*: Am. J. Hyg., 1952, *56*, 294.

[7] Parker, R. T., *et al.*: Proc. National Meeting American Federation for Clinical Research, Abstract 104, Clinical Research Proceedings, 1953, *1*, 100.

fifteen days after the drug was discontinued. The natural course of typhoid fever is approximately six weeks; hence, the treatment would be regarded as well beyond the natural course. Reapplication of the antimicrobial results in amelioration of the acute manifestations and ultimate recovery.

It has not been possible to utilize *in vitro* laboratory tests as an indicator reaction of immunity, since there is little correlation between the typhoid "O" or "H" agglutinin and host resistance.[3]

Present concepts of drug administration in typhoid fever are similar to those mentioned for early rickettsial infections. That is, the intermittent application of the drug, with appropriate rest periods, results in supression of the organism during treatment and multiplication of the organisms with subclinical disease during the intervals. It is now established that the relapse in typhoid fever occurs in approximately fifteen days after the drug is discontinued.[3, 8] Observations are now being made with regimens which provide for five-day treatment courses and intervals of approximately eight days. Three five-day treatment regimens are now being practiced.[4] The plan of rest periods, allowing antigenic stimulation, and clinical suppression with antimicrobials at crucial periods has much in its favor.

An additional method of providing antigenic stimulation is the administration of killed typhoid vaccine.[3] Conceivably, combined chemotherapy and immunization may find application in the field of tuberculosis.

Certain of the concepts mentioned for the rickettsial infections and typhoid fever apply in tularemia. Relapse ensues in tularemic patients treated quite early in the clinical infection, whereas recrudescence is much less common when therapy is given after the disease has been under way for several weeks.[9, 10]

Certain laboratory studies are pertinent.[11] It was observed that prompt short-term treatment (three days) and delayed short-term treatment of mice experimentally infected with *Pasteurella tularensis* resulted in death. Immediate long-term treatment (twenty days) allowed infected mice to recover, but they did not become immune, as shown by their inability to withstand a challenge infection. However, delayed long-term treatment resulted in recovery of the animals, and approximately 50 per cent were shown to develop immunity by virtue of their ability to withstand a challenge infection.

One cannot draw a direct analogy between tuberculosis, the rickettsial infections, and Gram-negative infections and propose that the concepts of intermittent or block therapy are translatable. However, short, intermittent therapeutic regimens are utilized for treatment of tuberculous patients,[12] and suggestions have been made concerning alternation of therapeutically effective

[8] El Ramli, A. H.: Lancet, 1950, *1*, 618.

[9] Parker, R. T., *et al.*: J. A. M. A., 1950, *143*, 7.

[10] Keefer, C. S.: J. A. M. A., 1946, *132*, 4.

[11] Snyder, M. J., *et al.*: The effect of antibiotic dosage schedule upon the development of immunity in mice to *Pasteurella tularensis*, presented at the annual meeting for the Society of American Bacteriologists, May, 1954.

[12] Waring, J. J.: Chicago M. Soc. Bull., October, 1952.

drugs. Any implication of similarity between the clinical situations discussed would possibly only apply with the problems related to primary or first infection tuberculosis.

The facts remain that, when suppressive chemotherapeutic drugs are used quite early in the course of rickettsial and certain Gram-negative infections, the development of host defense or immunity in the broad sense is delayed. There is unmistakable evidence that the appropriate therapy does not succeed in *eradicating* the offending microbe from the host, and this microbe may re-emerge from the confines of the cell at a later date and, in the presence of waning or insufficient immunity, again provoke disease. It has been determined on the basis of human observations, not on animal experimentation or *in vitro* serologic testing, that the time of relapse varies with the stage of disease when treatment is instituted and with each individual microbe; viz., relapse in rickettsial disease, six to eight days after stopping treatment[2]; typhoid fever, fifteen days;[3] tularemia, four to six days.[3] Better spacing of treatment by varying the time and duration with rest periods has resulted in more efficient host defense or immunity.

The disease organisms mentioned have at least one feature in common with *Mycobacterium tuberculosis*. They grow and multiply intracellularly.[10] Under certain circumstances, they are able to live in the cell for long periods of time without destroying the cell; yet at other times are capable of re-emerging from the cell to challenge the resistance of the host.

Could it be that wider variations of the intermittent regimens utilizing antituberculous drugs or their combinations would result in different host response, keeping in mind, of course, adverse alterations in patterns of bacterial susceptibility? One might consider longer periods of continuous therapy for several weeks, variable rest periods, and repeated drug courses. Certainly, the tubercle bacillus behaves differently and multiplies less actively than rickettsiae or *Salmonella typhosa*. Perhaps these observations have been made and such remarks are redundant. If not, certain clues are to be had by observations in experimentally infected animals with appropriate treatment intervals and analysis of the tissue reaction by histopathologic methods and antimicrobial bacterial susceptibility tests.

The acquired knowledge concerning rickettsial infections has come from observations by trial and error on human subjects with diseases, however, which were amenable to very efficient therapeutic control. It appears that immunity comes at a price dependent upon the degree of antigenic stimulation and host reaction which has transpired by the time specific therapy is instituted. One does not interfere too greatly with the natural forces of immunity if the timing is accurate.

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[10] MIDDLEBROOK, G., AND FREUND, J.: Mycobacteria, from *Bacterial and Mycotic Infections of Man*, ed. 2, edited by R. J. Dubos, J. B. Lippincott Company, Philadelphia, 1952, p. 324.

# *Notes*

## INDUCTION OF ARTIFICIAL PNEUMOTHORAX[1]

For forty years, the technique and the origin of an initial therapeutic pneumothorax have been discussed. When Dr. W. Perry Morgan[2] first presented the subject in 1914, he certainly did not realize that it would be the subject of an editorial in THE AMERICAN REVIEW OF TUBERCULOSIS in 1954.

This editorial[3] and recent correspondence[4] have called attention to the subject, even though artificial pneumothorax is not in vogue in the present-day therapy of pulmonary tuberculosis. The present writers take issue with the thesis that all initial pneumothoraces must be traumatic.[5] Various types of needles have been invented for the purpose of avoiding lung trauma.[6] However, the tissue-paper-like property of the pleura prevents mechanical separation. Some clinicians believe it impossible to induce an artificial pneumothorax without causing a traumatic pneumothorax.[7] In fact, it has been stated that just as satisfactory results might be achieved by the use of an ordinary sewing needle thrust through the chest wall and allowed to penetrate the visceral pleura.[8, 9]

In order to ascertain whether or not a nontraumatic artificial pneumothorax could be established, the writers tried to induce pneumothorax in 47 consecutive patients. These 47 patients were considered satisfactory candidates for pneumothorax therapy. It was to this extent that a selection of patients was made for this study. The day before and the day following initial pneumothorax, the vital capacity of each patient was recorded. The day following, a chest film in full expiration was made. The attempted pneumothorax was unsuccessful in 8 cases. However, in order to exclude the possibility that air might have leaked through the visceral pleura and that the writers were mistaken in the belief that complete symphysis existed, an expiratory chest film was taken the day following. In none of these 8 was a pneumothorax shown to be present.

In only one of the cases in which pneumothorax could not be established was there appreciable decrease in the vital capacity readings. In the successful attempts (39) there were 8 persons whose reduction of vital capacity was appreciably greater than the amount of air introduced.[10] It is realized that vital capacity readings are not a critical test because of the subjective factor. Nevertheless, such a test does give some idea of the reduction of lung capacity caused by air in the pleural space. There were only 4 cases, according to the roentgenographic findings, in which there was more air in the pleural space than had been introduced through the needle.

The technique was as follows:

> A large, short-bevel needle, No. 17 or No. 16, is attached to an ordinary 2 cc. Luer syringe filled with 2 per cent procaine. The plunger of the syringe should be very loose.

[1] Presented before the California Tuberculosis and Health Association on April 2, 1952.
[2] Morgan, W. Perry: Lancet, 1914, *2*, 90.
[3] Vysniauskas, C.: Am. Rev. Tuberc., 1954, *69*, 121.
[4] Weiss, W.: Am. Rev. Tuberc., 1954, *69*, 844.
[5] Dooneief, A. S., and Piccagli, R. W.: Am. Rev. Tuberc., 1949, *60*, 557.
[6] Hartman and Markgraf: Tuberkulosearzt, 1948, *H11*, 743.
[7] Tehertkoff, I. G.: Quart. Bull. Sea View Hosp., 1936, *1*, 398.
[8] Selikoff, I. J., and Robitzek, E. H.: Dis. of Chest, 1948, *14*, 475.
[9] Moyes, E. N., and Scott, J. K.: Lancet, 1952, 1, 1275.
[10] More than 150 cc. decrease in vital capacity.

TABLE 1

THE VITAL CAPACITY BEFORE AND AFTER INDUCTION OF PNEUMOTHORAX

| | Vital Capacity Before | Vital Capacity After | Amount of Air | Change in Vital Capacity |
|---|---|---|---|---|
| 1 | 1,100 | 1,200 | 300 cc. | +100 |
| 2 | 2,300 | 2,250 | 400 cc. | −50 |
| 3 | 1,850 | 1,850 | Unsuccessful | 0 |
| 4 | 2,200 | 1,800 | 400 cc. | −400 |
| 5 | 2,200 | 2,250 | 350 cc. | +50 |
| 6 | 2,400 | 2,350 | 400 cc. | −50 |
| 7 | 2,250 | 2,250 | 400 cc. | 0 |
| 8 | 2,200 | 2,200 | 400 cc. | 0 |
| 9 | 2,250 | 2,000 | 350 cc. | −250 |
| 10 | 2,400 | 2,750 | Unsuccessful | +350 |
| 11 | 2,000 | 1,900 | 400 cc. | −100 |
| 12 | 3,050 | 2,675 | 350 cc. | −375 |
| 13 | 3,000 | 2,900 | 400 cc. | −100 |
| 14 | 2,950 | 2,500 | 400 cc. | −450 |
| 15 | 2,050 | 2,000 | 400 cc. | −50 |
| 16 | 3,400 | 3,200 | 500 cc. | −200 |
| 17 | 3,400 | 3,000 | 400 cc. | −400 |
| 18 | 1,800 | 2,000 | 400 cc. | +200 |
| 19 | 3,450 | 2,925 | 400 cc. | −525 |
| 20 | 2,200 | 2,200 | 350 cc. | 0 |
| 21 | 2,900 | 2,450 | 450 cc. | −450 |
| 22 | 1,100 | 1,750 | 400 cc. | +650 |
| 23 | 2,300 | 1,750 | 400 cc. | −550 |
| 24 | 2,700 | 2,700 | 400 cc. | 0 |
| 25 | 2,600 | 2,575 | Unsuccessful | −25 |
| 26 | 3,475 | 2,775 | 500 cc. | −700 |
| 27 | 2,800 | 1,975 | 400 cc. | −825 |
| 28 | 1,250 | 1,200 | Unsuccessful | −50 |
| 29 | 3,200 | 2,450 | 400 cc. | −750 |
| 30 | 3,250 | 2,900 | 500 cc. | −350 |
| 31 | 3,000 | 2,600 | 500 cc. | −400 |
| 32 | 2,100 | 2,100 | Unsuccessful | 0 |
| 33 | 3,100 | 3,100 | 300 cc. | 0 |
| 34 | 2,600 | 2,650 | Unsuccessful | +50 |
| 35 | 3,500 | 2,800 | 500 cc. | −700 |
| 36 | 2,900 | 2,600 | 400 cc. | −300 |
| 37 | 2,000 | 1,250 | 400 cc. | −750 |
| 38 | 3,500 | 3,500 | 400 cc. | 0 |
| 39 | 2,400 | 2,100 | Unsuccessful | −300 |
| 40 | 1,500 | 1,700 | 400 cc. | +200 |
| 41 | 2,800 | 2,350 | 400 cc. | −450 |
| 42 | 2,500 | 2,500 | Unsuccessful | 0 |
| 43 | 1,600 | 1,300 | 400 cc. | −300 |
| 44 | 1,800 | 1,400 | 300 cc. | −400 |
| 45 | 2,300 | 1,800 | 400 cc. | −500 |
| 46 | 750 | 400 | 150 cc. | −350 |
| 47 | 3,200 | 2,200 | 400 cc. | −1,000 |

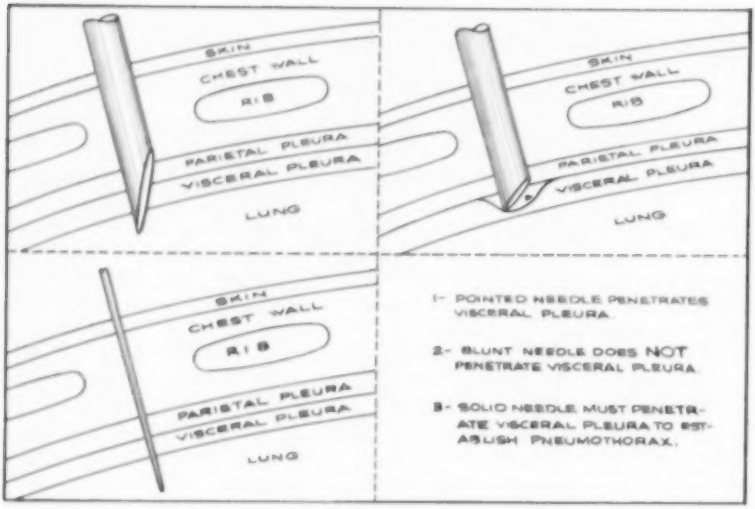


FIG. 1

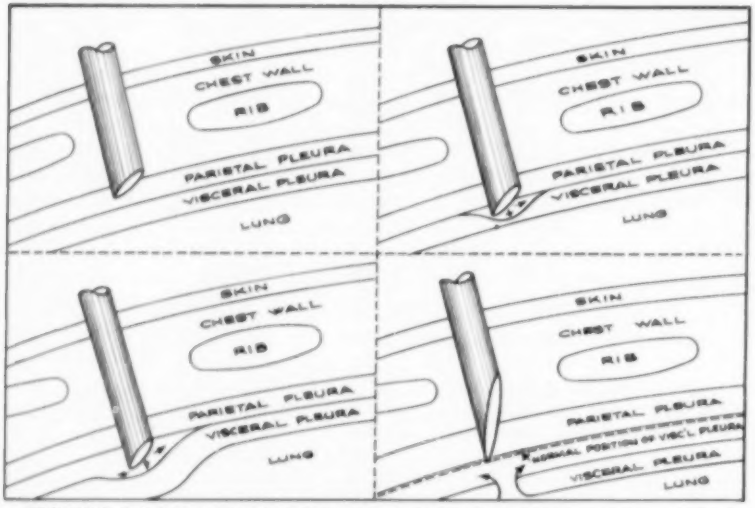
SKIN
CHEST WALL
RIB
PARIETAL PLEURA
VISCERAL PLEURA
LUNG
NORMAL POSITION OF VISC'L PLEURA
PROCAINE & AIR ACT TO SEPARATE LAYERS OF PLEURA WITH SHORT BEVEL NEEDLE. LONG BEVEL CUTS VISCERAL PLEURA

FIG. 2

First a sharp needle is used to cut a hole in the skin.[11] This prevents a particle of skin from blocking the final needle at the time of introduction of air, and enables the blunt needle to pass through the skin without difficulty. The blunted No. 17 needle attached

[11] One of the writers prefers to use a scalpel blade to cut the skin.

to the syringe, with approximately 1 cc. of procaine and 1 cc. of air in the syringe, is then passed through the chest wall and through the parietal pleura. As the normal pleural pressure is less than atmospheric, the most minute opening in the parietal pleura will permit the procaine solution to be drawn into the pleural space, indicated by the falling of the plunger of the syringe. The pneumothorax apparatus is then connected. If air should be drawn into the pleural space while the pneumothorax apparatus is being connected, it is not a cause for concern because it aids in separation of the pleura.

The writers believe that the concept that an artificial pneumothorax cannot be induced without producing a traumatic pneumothorax is false, as the present results have shown. Moreover, it is poor teaching to tell an intern or student who is learning technique that, no matter how careful he is, the procedure will only result in trauma. This encourages carelessness.

It has been stated[2] that the smaller the needle used, the smaller the resulting traumatic pneumothorax because the collapse of the lung is proportional to the size of the hole made in the visceral pleura. Therefore, it has been advocated that a very small needle be used. If it is assumed that all initial pneumothoraces are traumatic, then a small needle should be used. However, when it is assumed that initial pneumothoraces need not be traumatic, then the use of the large needle becomes possible and, indeed, obligatory.

It is believed that a nontraumatic pneumothorax is achieved by this method in the following way. The large, blunt needle, after passing through the parietal pleura, allows a cushion of procaine to form. This cushion, or wedge, precedes the needle and separates the two layers of pleura. The needle is thus prevented from touching the visceral pleura (*see* figures).

The use of the large needle permits the fluid, and later the air, more quickly to enter the pleural space, further lessening the chance of injury to the visceral pleura. The blunt needle aids also in preventing pleural trauma because with a short bevel the forward edge of the needle passes the parietal pleura and the needle opening immediately follows. In contrast, with the long-bevel needle, the forward edge of the needle will pass a considerable distance through the parietal pleura and traumatize the visceral pleura before the needle opening will have passed through the parietal pleura (*see* figures).

*In summary*: A method for the induction of artificial pneumothorax has been described. It is believed that this method lessens the chances of traumatic pneumothorax and that it is possible and probable, as the data show, to establish an initial pneumothorax equal in size to the amount of air introduced through the needle.

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December 7, 1954

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## A POSSIBLE ANTAGONISTIC EFFECT BETWEEN PNEUMOTHERAPY AND CHEMOTHERAPY

*To the Editor of The American Review of Tuberculosis:*

Woodruff and his associates of Maybury Sanatorium in a letter to the editor (Am. Rev. Tubere., 1954, *70*, 533) suggest that collapse therapy might interfere with chemotherapy on the premise that the two forms of therapy operate on contradictory principles. The effectiveness of selective collapse, they point out, depends primarily on its ability to materially cut down the supply of oxygen reaching the tubercle bacillus in the diseased area; whereas, the effectiveness of chemotherapy depends on an intact circulation by which the therapeutic agent may be brought to the diseased part. Selective collapse, however, which for all practical purposes means atelectasis maintained for a long time, in bringing about the desired oxygen deficiency at the site of disease also causes a simultaneous marked decrease in blood flow through the same collapsed portion of the lung. Hence, they emphasize, selective collapse therapy if successful may tend to inhibit specific drug therapy by way of the blood stream. It would seem, therefore, they conclude, that the two forms of therapy are antagonistic to each other and don't mix.

The National Tuberculosis Association in the October, 1954, release of Scientific Articles on Tuberculosis, distributed through the Pennsylvania Trudeau Society, expressed this same thought more dramatically:

"One plus one equals—zero."

"Substitute drugs for the first 'one' and collapse of the lungs for the second and the two may add up to nothing in the treatment of tuberculosis."

The above Maybury conclusions, reached on an admittedly pragmatic basis, however, are no justification whatever for abandoning the simultaneous use of collapse therapy and chemotherapy. Careful clinical observation and a little anatomical reflection will readily convince one that the two therapies, although each works in a different manner to bring about cure, are not only *not* antagonistic but complement and supplement each other to the great benefit of the patient.

The weakness in the reasoning of the Maybury staff is in underestimating the interdependent role of the double blood supply of the lung in maintaining adequate circulation throughout the lung in the event of partial or complete obstruction of either the pulmonary or bronchial circulations. Blood circulation to the lungs is not as simplified a matter as the concept implied by the writers would indicate.

True, the pulmonary artery alone supplies capillaries to the respiratory tissue of the lung. The air spaces and alveoli contain no bronchial vessels. However, there is a well-recognized rich capillary anastomosis between the respiratory (pulmonary) and the systemic (bronchial) vessels in the walls of the respiratory bronchioles (Miller, H. S.: The Lung, Charles C Thomas, Springfield, Illinois, 1937). In addition, there are important communications between the bronchial and pulmonary systems, through anastomoses larger than capillaries (Tobin, E. E.: Surg., Gynec. & Obst., 1952, *95*, 741). Tobin and Zariquiey (M. Radiog. & Photog., 1953, *29*, 9) found direct communications as large as 200 to 250 microns in diameter between the branches of these two arteries deep within the lung, in the visceral pleura, and in the walls of the secondary bronchi and their branches.

These same writers also demonstrated arteriovenous shunts, larger than capillaries, as normally present between the pulmonary artery (and their connections with the bronchial arteries) and the pulmonary veins.

Communications between the two systems of veins, of course, are known to be very extensive. The bronchial veins form a plexus around the bronchi which normally drain into the pulmonary veins intrapulmonically and into the azygous veins, extrapulmonically. At various intervals, however, the venous plexus draining into the pulmonary veins connects with branches of the venous plexus which drain upward into the azygous system by way of the extrapulmonic bronchial veins (Tobin).

Sufficient has been said to indicate that many potential channels are normally available for the free circulation of blood between the pulmonary and systemic vessels and that the pulmonary capillaries of the alveolar walls normally contain blood derived from both systems. The amount of blood from the bronchial component, however, is not believed to be large, for the bronchial circulation contributes not more than 1 per cent to the total pulmonary circulation (Best and Taylor: Physiological Basis of Medical Practice, 1950, p. 345). But under certain physiologic and pathologic conditions, these communicating channels may enlarge sufficiently to divert considerable quantities of blood to either system. It is possible, therefore, under certain conditions for the bronchial arteries to take over part of the function of the peripheral branches of the pulmonary artery and for the bronchial veins to return part of the blood from the lungs to the right side of the heart in the event of obstruction of the pulmonic venous flow (Tobin).

The mere fact, then, that the circulation in the pulmonary system is slowed or reduced to zero in the atelectatic lung does not warrant the assumption that there is no important blood circulation in the atelectatic lung by way of the bronchial system of vessels. Were that true, the nutrition of the atelectatic lung would be seriously interfered with to the point of gangrene. All available experimental and clinical evidence on the atelectatic lung, however, is to the contrary.

In resected human atelectatic lungs which have remained in complete atelectasis for periods up to twenty-six years following stenosis of the main bronchus resulting from traumatic rupture of the bronchus, there was no gross or microscopic evidence of fibrosis or degenerative vascular disease, no evidence of infection or bronchiectasis. The bronchial glands, bronchi, smooth muscle, cartilage, arteries, lymphatics, nerves, and alveoli, all appeared almost unchanged histologically (Webb, W. R. and Burford, R. H.: Arch. Surg., 1953, *66*, 801). The same has been found true in experimental atelectasis (Bjork, V. O., and Salén, E. F.: J. Thoracic Surg., 1950, *20*, 933). In fact, Webb and Burford (*see* above) were recently able to re-expand and restore to full normal function dog lung which had been rendered atelectatic for months by transecting a main stem bronchus and suturing the divided ends, after the same ends were later opened and anastomosed. In the human, of course, it is an every-day experience to see a re-expanded pneumothorax lung resume good function after it has been maintained in continuous collapse for years.

The excellent morphologic and functional preservation of atelectatic lung tissue, even after years of complete collapse, can only be explained on the basis that it is chiefly the pulmonic or respiratory circulation which is interfered with, the bronchial or nutritive circulation remaining more or less intact.

The reduced or negligible blood flow through the atelectatic lung is apparently due to the closing down of the capillary bed—vessels of the pulmonary circuit—around the empty alveoli, in the same way as in a resting part of an organ (Björk, V. O.: *see above*). The bronchial system, however, has no capillary vessels in the alveolar walls and, hence,

does not experience this same capillary shut down. Furthermore, the bronchial arteries—branches of the thoracic aorta—occupy a protected position within the lung. They are so embedded in the layer of connective tissue which surrounds the bronchi and their branches, it is virtually impossible to close them shut without injury to the bronchi. Bronchial circulation, therefore, remains intact in complete atelectasis and continues to supply oxygenated blood to the atelectatic pulmonary tissue. This was nicely demonstrated by Bjork (J. Thoracic Surg., 1953, *26*, 533). He observed that the mean value of oxygen saturation in the pulmonary artery in total atelectasis from complete bronchial stenosis was significantly higher than that in the pulmonary veins—a finding which could only be explained on "an admixture of blood from the bronchial arteries draining blood into the pulmonary artery in a reverse direction."

In the face of the negligible blood flow in the human lung rendered completely atelectatic for years because of complete bronchial stenosis, metabolites, enzymes, crystalloids, and all the other nutritive products found in blood can still be transported through the completely atelectatic lung by way of the lesser bronchial circulation and then diffuse to every cell in sufficient concentration to maintain such atelectatic tissue in unimpaired health for a period of many years. Thus, how can selective pneumotherapy, which in practice is neither total nor constant and not characterized by complete stenosis of the bronchi, prevent diffusible therapeutic agents, such as isoniazid, from reaching the collapsed part of the lung? Even relatively poorly diffusible therapeutic compounds, such as streptomycin, must circulate through all parts of the collapsed lung because of the important precapillary anastomotic communications between the bronchial and pulmonary vessels deep within the lung.

As a matter of practical experience, excellent results, better than ever and with fewer complications, can be achieved today through the intelligent and skilled use of simultaneous selective pneumotherapy and chemotherapy in selected cases. To speak seriously of a possible antagonistic effect between pneumotherapy and chemotherapy just doesn't make sense.

Sincerely yours,
J. W. Cutler

Wawa Chest Hospital
Wawa, Pennsylvania

November 22, 1954

## AMBULATION OF TUBERCULOUS PATIENTS UNDER PROTECTION OF CHEMOTHERAPY

*To the Editor of The American Review of Tuberculosis and Pulmonary Diseases:*

In the December, 1954, *American Review of Tuberculosis*, Dressler and associates present their argument for "ambulation of patients with pulmonary tuberculosis under protection of chemotherapy." Data on 96 patients with advanced disease treated with 4 to 8 mg. of isoniazid per kg. of body weight, alone or in combination with streptomycin, 1 gm. every three days, for six to eighteen months and "ambulated . . . soon after admission to the National Jewish Hospital" are presented.

This paper records the reasons for the present trend toward reduction of bed rest during the prolonged chemotherapy of pulmonary tuberculosis. After carefully reviewing the activity schedules prescribed for their patients, it is my opinion that patients in at least three hospitals in the Saranac Lake area, the Veterans Administration Hospital at Sunmount, the New York State Tuberculosis Hospital at Ray Brook, and Trudeau Sana-

torium, have done well on quite comparable rest and activity programs for the past two years or so. In short, the difference between the National Jewish Hospital program of "ambulation" and other programs of "rest" is apparently a matter of semantics.

While the authors are careful not to draw final conclusions from their findings, they seem to draw a conclusion indirectly when they say "as a result of this study, it is believed that the vast majority of patients with pulmonary tuberculosis, advanced as well as minimal, no longer have to 'acquiesce' to the disease. They need only acquiesce to chemotherapy and surgery; and this is probably most effectively achieved in a hospital. . . ." I am convinced that a minimum of three to five years' observation after *completion* of therapy is needed to evaluate any therapy for pulmonary tuberculosis. On the basis of actual experience, we can now begin to have confidence in the late results in patients whose disease has become inactive after prolonged streptomycin-PAS-rest therapy, integrated with collapse and resection. It has been less than three years since the introduction of isoniazid. As a consequence we have only a handful of patients who have completed regimens including isoniazid and none to my knowledge without some rest.

I share the authors' enthusiasm for the results of chemotherapy to date, and I hope we may be able to reduce rest even more than we have so far. Until more facts are in, I believe we should continue to teach our patients to respect the disease, i.e., to acquiesce.

Yours faithfully,
ROGER S. MITCHELL

TRUDEAU-SARANAC INSTITUTE
TRUDEAU, NEW YORK
December 21, 1954

# *Books*

ANATOMY OF THE BRONCHOVASCULAR SYSTEM. Its Application to Surgery. By George L. Birnbaum. Pp. 300, with illustrations, Year Book Publishers, Inc., Chicago, Illinois, 1954, Price, $15.00.

It was no longer ago than 1940 that Churchill (Surgery, vol. 8) stated that: "Resection of the middle lobe alone by individual ligation technique is possible, but not recommended. The bifurcation of the middle lobe bronchus occurs at a high level and the blood supply is so complicated that tourniquet technique had best be employed."

The dissatisfaction with the gross removal of large volumes of functioning pulmonary tissue as the easiest way to remove a small component of diseased lung led to the attempts pioneered by Churchill and Belsey to divide the lung into bronchovascular segments which could be individually resected without sacrifice of adjacent normal lung parenchyma. The resultant importance of the detailed anatomy of the smaller bronchus, arteries, and veins led to extensive anatomic studies.

These studies, by the author, by Boyden and Scannell, by Liebow and associates form the hard core of the present volume. Dr. Birnbaum confesses that he succumbed to the temptation to expand his book to include the ramifications implicit in a broad consideration of his subject. There is, for instance, a fairly detailed section on congenital heart disease. The entire book is well illustrated with original drawings and reproductions from other works. Sections on bronchovascular anatomy are written in large part as detailed anatomic texts, and this reader's hostile reflex to the complication of anatomic nomenclature by a codification system like Boyden's is not appeased by the author's introduction of a variation of his own. Greater use of photographs and drawings of dissections and injections, with much of the present text incorporated in the legends, might make for clearer reading. The sections on the lymphatics and the nerve supply of the lungs might well have been modernized and expanded at the expense of chapters on experimental cardiovascular surgery and extracorporeal shunts. A fairly detailed "outline of pulmonary resection techniques" is an interesting approach in surgical teaching and useful in its logical form to the thoracic surgeon in training. This section is not illustrated.

The manner of the writing of much of the book is of interest. It consists essentially of abstracts of papers by key workers on given subjects, with reproductions of the original illustrations. To this is added the pertinent supporting or contrary experience and reasons of other writers and at times the result of a recent inquiry to the writer by Dr. Birnbaum. This method, coupled with extensive quotation of pertinent case reports from the literature, makes for easy and informative reading and allows for a combination of broad review and specific detail. It is reminiscent of the texts of an earlier day. However, thoracic surgery may still be young enough for this approach. The bibliography is excellent, and there is both a subject and an author index.

MARK M. RAVITCH
New York, New York

AN OUTLINE OF PRESENT DAY THORACIC SURGERY. By Robert I. Carlson. Pp. 158, Educational Publishers, Inc., St. Louis, Missouri, 1954.

In the introduction the author states: "This outline has been prepared primarily for the benefit of medical students, internes and residents who have an interest in the field of Thoracic Surgery. It may be of some interest to practitioners who have not had formal training in the field, but it is not designed for thoracic surgeons of experience. No attempt

is made to exhaustively review the subject of Thoracic Surgery and its ramifications; its purpose is to serve as a starting out point in a study of the field for those who are interested."

As in any outline, this is mainly skeleton with very few soft parts being included. There are no illustrations of any kind, and the student must refer to anatomy and physiology texts for better understanding of the chapters on surgical anatomy and pulmonary physiology. Congenital, traumatic, acquired, and neoplastic diseases of the thoracic cage, diaphragm, lungs, and mediastinal structures are dealt with systematically. Recent advances in the surgery of the heart and great vessels are outlined. In the section on tuberculosis the medical aspects of the disease are well covered, and the indications and contraindications for the various types of surgical procedures are presented. On controversial subjects the opinions of various authorities are quoted.

This outline should also be of assistance to the general surgeon who is infrequently called upon to do chest surgery. The bibliography is excellent and provides a ready means of supplementing the outline. Unfortunately the type of looseleaf binding employed is not adequate to permit the pages to be turned easily and smoothly.

George R. Holswade
New York, New York

Tuberculosis in Childhood and Adolescence. By F. J. Bentley, S. Grzybowski, and B. Benjamin. Pp. 259, National Association for the Prevention of Tuberculosis, London, 1954, Price, $5.00.

This book is a report of the authors' experiences in the treatment of tuberculous children at High Wood Hospital near London, England. The material discussed is limited to the types of cases seen and the methods of treatment used by the authors. In other words, *Tuberculosis in Childhood and Adolescence* is a monograph rather than a textbook. This type of book has many advantages: the presentation is interesting and thought provoking; the great variety of clinical material, the long period of observation in the hospital, and the excellent follow-up (more than 90 per cent) make this report outstanding to those interested in the diagnosis and prognosis of tuberculosis in children.

At this time when there is so much discussion about the advisability of treating primary tuberculosis even in the absence of symptoms, it is refreshing to read the conservative statement made by the authors that "antibiotics do not exert any pronounced effect on the usual course of simple primary disease. Radiological progress of primary lesions appears just as slow in cases given antibiotics as in those from which they are withheld. There is no unusual diminution in the size of the mediastinal glands and the appearance of the primary focus remains unaffected. Segmental lesions also generally run their usual course towards progressive contraction. The endobronchial pathology seen in cases with segmental lesions does not appear to clear more quickly under the influence of antibiotics. Common early complications of primary tuberculosis—pleural effusions and segmental lesions—continue to arise in children treated with antibiotics and we are unable yet to say whether their incidence is in any way affected." However, in common with other observers, the authors have not seen hematogenic complications develop in children receiving antimicrobial therapy and suggest that a controlled trial utilizing large numbers of children may be advisable, the results to be assessed only after an adequate period of follow-up. *Tuberculosis in Childhood and Adolescence* is highly recommended to those interested in this phase of tuberculosis.

Edith M. Lincoln
New York, New York

## BOOKS RECEIVED

Die Tuberkulose in der Ärztlichen Praxis. Edited by A. Wernli-Hassig. Pp. 154, S. Karger, Basel and New York, 1954, Price. $5.55 (American representative: Albert J. Phiebig, Post Office Box 352, White Plains, New York)

The Clinical Physiology of the Lungs. By Cecil K. Drinker. Pp. 84, Charles C Thomas, Springfield, Illinois, 1954, Price, $5.50.

The History and Conquest of Common Diseases. Edited by Walter R. Bett. Pp. 334, University of Oklahoma Press, Norman, Oklahoma, 1954, Price, $4.00.

Behringwerk-Mitteilungen. Edited by E. v. Behring. Pp. 127, N. G. Elwert, Universitäts-und Verlagsbuchhandlung, Marburg-Lahn, Germany.

Sandoz Atlas of Haematology. Pp. 91, with 44 plates, Sandoz Blood Atlas, 68 Charlton, St., New York, Price, $7.00.

Das Transversale Schichtverfahren. By A. Gebauer and A. Schanen. Pp. 313, Georg Thieme Verlag, Stuttgart, 1955 (American representative: Intercontinental Medical Book Corporation, New York 16, N. Y.), Price, $23.20.

Primo-Infection et Réinfection dans la Tuberculose Pulmonaire. By G. Canetti. Pp. 261, Editions Medicales Flammarion, 22, rue de Vaugirard, Paris, 1954.

Perspectives and Horizons in Microbiology. Edited by Selman A. Waksman. Pp. 220, Rutgers University Press, New Brunswick, New Jersey, 1955, Price, $3.50.

# *American Trudeau Society*

**Medical Section of the National Tuberculosis Association**

## NOTICES

### FORTY-FIRST SESSION OF THE TRUDEAU SCHOOL OF TUBERCULOSIS—1955

Although the Trudeau Sanatorium has closed, the Trudeau School will be held as in the past, utilizing the staff, facilities, and skills of the Trudeau research laboratories, of the many sanatoriums in the area, and of the tuberculosis specialists of Saranac Lake. A four-week course will commence on June 1, 1955, at Saranac Lake, New York.

*Schedule of Instruction* includes the history, etiology, epidemiology, pathology, bacteriology, physiology, biochemistry, diagnosis, and treatment of tuberculosis; other chronic lung disorders, with special emphasis on pneumoconioses; clinical and bedside teaching.

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*Note:* Since 1939 the Trudeau School has been supported by grants from the Lillia Babbitt Hyde Foundation, of which Mr. Charles C. Harris is President.

*For Schedule and Other Information Write to Secretary*, Trudeau School, Box 200, Trudeau, New York.

### ANNUAL MEETING OF THE EASTERN SECTION OF THE AMERICAN TRUDEAU SOCIETY

The annual clinical meeting of the Eastern Section of the American Trudeau Society will be held at the Sheraton-Biltmore Hotel, Providence, Rhode Island, on October 21 and 22, 1955.

Members and interested physicians are invited to submit abstracts of papers for consideration by the Program Committee for this meeting. Abstracts should be submitted in triplicate to M. G. Carter, M.D., Chairman of Program Committee, 614 Orange Street, New Haven, Connecticut. All abstracts must be received prior to May 15, 1955.

## ERRATUM

In the Abstract Section of Volume 71, No. 2, 1955, on page 62, "Summary of Reports of the Member States, 1950–1953, Pan American Sanitary Bureau," the second sentence in the sixth paragraph should be changed to read as follows: There were 3,029 *new tuberculosis suspects* among 543,410 persons who were examined, instead of: There were 3,029 new cases among 543,410 persons who were examined.

Wedge resection of tuberculoma.


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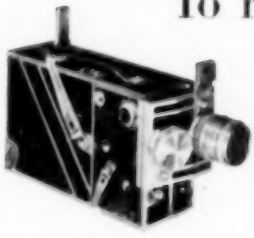

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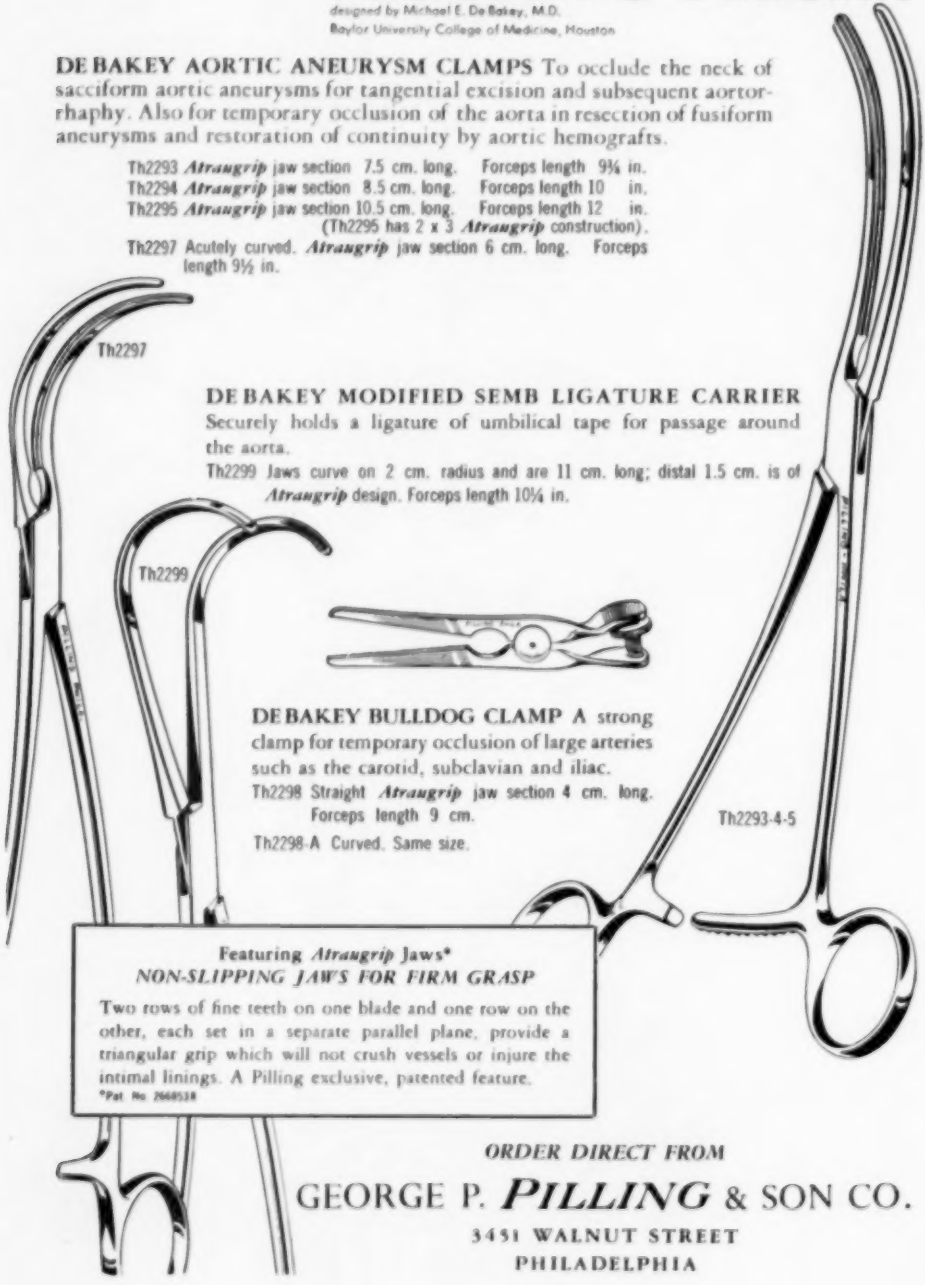


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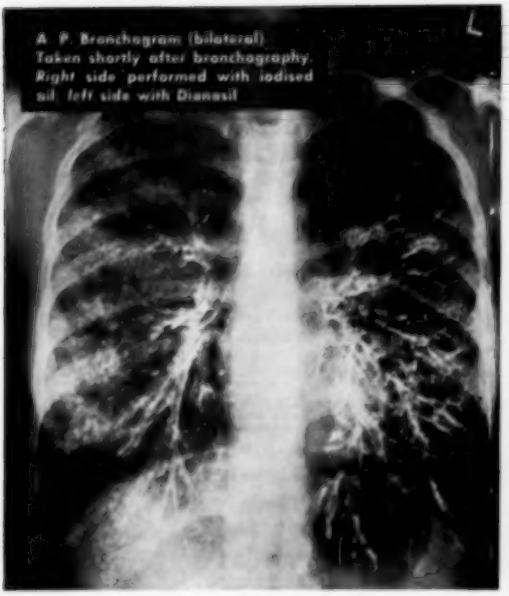
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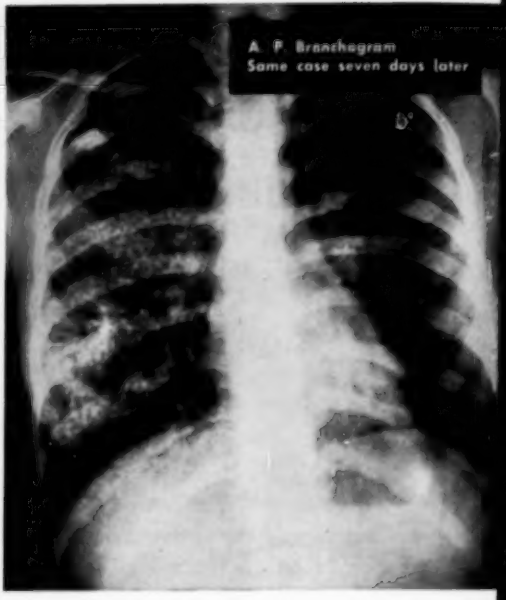


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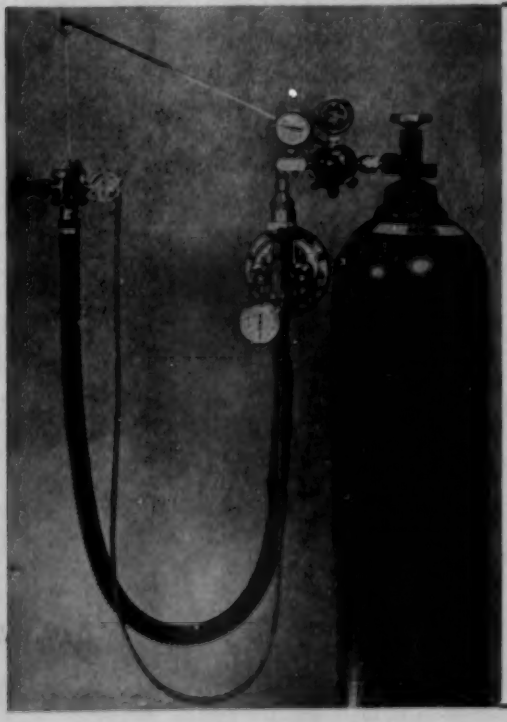

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| 17 | 24 | 8.5 Gm. |
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- *PARASAL SODIUM tablets,* 0.69 Gm. (eqd. P.A.S.).

*References*

*(1) V.A. Quarterly Prog. Report, April '53*

*(2) V.A. Quarterly Prog. Report, Oct. '54*

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